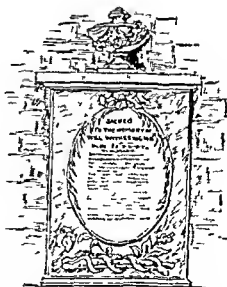


William
Withering
1741-1799

First in the rational
use of digitalis



After many years of careful study William Withering published his *Account of the Foxglove and Some of its Medicinal Uses* in 1785. Digitalis remains as the most valuable cardiac drug ever discovered. The general principles laid down by Withering with few exceptions, guide the modern physician in the administration of digitalis.

THE DIAGNOSIS and TREATMENT OF CARDIOVASCULAR DISEASE

~~Edited~~ *edited by*

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TABLE OF CONTENTS

CHAPTER	PAGE
XXXI The Clinical Efficacy of Various Digitalis Preparations	1001
Indications	1001
Method of Administration	1004
Choice of Preparation	1007
Method	1011
Comment	1018
XXXII The Prevention and Relief of Heart Disease As A Public Health Problem	1023
Etiology	1023
Prevention	1025
The Origin and Work of the American Heart Association	1028
Historical	1028
Activities of the Association	1038
Meetings	1038
Scientific Exhibits	1039
Publications	1039
Other Educational Activities	1040
Clinics	1040
Method of Work	1041
Officers of the American Heart Association for 1940	1042
Board of Directors	1042
Committee on Education and Publicity	1043
Subcommittees of Committee on Education and Publicity	1043
Committee on Charts and Exhibits	1043
Committee on Films and Slides	1043
Committee on Leaflets and Pamphlets	1043
Committee on Modern Concepts of Cardiovascular Disease	1043
Committee on Program for Scientific Sessions	1043
Committee on Membership	1043
Committee on Cardiac Clinics	1044
Committee on Rheumatic Diseases	1044
Advisory Group to Committee on Rheumatic Diseases	1044
Committee on Activities	1044
Committee to Study Coronary Artery Disease	1044
Committee on Nominations	1044
Committee to Cooperate with the American Board of Internal Medicine	1044
Committee on Therapy	1045
Committee on Standardization of Precordial Leads	1045
Committee on Standardization of Blood Pressure Readings	1045
Section For the Study of the Peripheral Circulation	1045
Officers	1045
Committee on Nominations and Membership	1045
Committee on Program for Scientific Sessions	1045
Committee on Nomenclature	1045
Diseases of Extremities	1045
Hypertension Nephritis and Associated Diseases of Blood Vessels	1045
Committee on Abstracts	1046
Committee on Standardization of Vascular Clinics	1046
Past Officers of the American Heart Association	1046
Aims	1046

CHAPTER	PAGE
XXXXIII The Cardiac in Industry	1018
Training in Sheltered Workshops	1057
Conclusions	1057
XXXXIV Congestive Heart Failure	1060
Pathogenesis and Mechanism	1060
Symptoms and Signs	1063
Complications and Sequelae	1065
Differential Diagnosis	1065
Prognosis	1066
Therapy	1067
Aim of Treatment	1067
Rest	1068
Sedatives and Hypnotics	1070
Digitalis	1071
<i>Digitalis Series of Drugs</i>	1071
Other Drugs of <i>Digitalis Series</i>	1082
Other Cardiac Drugs	1081
Diet	1092
Cathartics and Laxatives	1097
Venesection	1099
Paracentesis	1100
Drainage of Subcutaneous Edema	1100
Surgical Procedures	1101
Treatment of Complications	1102
Treatment of Associated Diseases	1105
Aftercare	1108
Psychotherapy	1110
Prevention	1110
XXXXV Left Ventricular Failure and Paroxysmal Cardiac Dyspnea	1112
Left Ventricular Failure	1112
Acute Paroxysmal Cardiac Dyspnea (Cardiac Asthma)	1113
Incidence	1114
The Attack	1115
Precipitating Factors	1115
Prognosis	1116
Therapy	1117
Left Ventricular Failure in General	1117
Paroxysmal Cardiac Dyspnea	1117
XXXXVI Effects of Digitalis on the Electrocardiogram	1130
Introduction	1130
Effects of Digitalis on T Wave and S T Segment of Electrocardiogram	1130
Influence of Digitalis on T Waves and S T Segments of Normal Hearts	1131
Stage I	1131
Stage II	1131
Stage III	1132
Stage IV	1132
Effects of Digitalis on T Waves of Badly Diseased Hearts	1131
Effects of Digitalis on T Waves in Different Types of Hearts	1131
Effects of Digitalis on P Wave of Electrocardiogram	1136
Effects of Digitalis on Rate Rhythm and Mechanism of the Heart	1137
Influence on the Cardiac Rate During Normal Sinus Rhythm	1137
A V Rhythm and A V Dissociation	1137
Atrial Fibrillation and Flutter	1139
A V Heart Block	1139
Relation to Extrasystolic Disturbances	1140
Ventricular Paroxysmal Tachycardia	1140
Effects of Digitalis Upon the Electrocardiogram of Preordial Leads	1142

CHAPTER	PAGE
Changes in the R S T in Association with a Large Initial Downward Deflection	1143
Deviation of R S T in Association with Small or Absent Initial Downward Deflection	1143
XXXXII Surgery of the Heart and Pericardium	1145
Introduction	1145
Classification of Heart Diseases	1147
Compression of the Heart	1148
Physiology	1148
Acute Compression Triad	1150
Chronic Compression Triad	1152
Trauma	1153
Penetrating Wounds of the Heart	1153
Diagnosis	1154
Treatment	1154
Nonpenetrating Wounds or Contusions of the Heart	1157
Incidence of Cardiac Contusions	1161
Symptoms and Diagnosis	1161
Treatment	1164
Hemopericardium	1164
Purulent Pericarditis	1165
Cardiac Compression Due to Scars	1169
Etiology	1169
Diagnosis	1170
Operation for Removal of Compression Scars	1171
Postoperative Care	1172
Results Obtained After Resection of Compression Scars	1173
Ligation of the Patent Ductus Arteriosus	1174
Selection of Patients	1175
The Operative Procedure	1176
Results After Ligation	1177
The Production of a Collateral Blood Supply to the Heart	1178
Experimental	1179
Vascularized Grafts for Coronary Artery Sclerosis	1179
Results of the Beck Operation	1180
Vascular Anastomoses Produced by Chemical Agents	1180
Ligation of Coronary Veins for Coronary Sclerosis	1180
Resuscitation of Heart from Standstill and from Ventricular Fibrillation	1181
First Stage in Resuscitation	1181
Second Stage in Resuscitation	1182
Operations on Cardiac Valves	1182
XXXXIII Relief of Pain in Angina Pectoris by Paravertebral Sympathetic Block with Alcohol	1185
Anatomy and Physiology	1185
Blocking of Sensory Pathways	1186
Technic	1188
Results and Sequelae	1192
XXXXIV Use of Quinidine in Cardiac Irregularities	1195
Introduction	1195
Action of the Drug	1196
Indications	1196
Contraindications	1197
Types of Arrhythmias	1199
Methods of Administration	1201
Temporary and Enduring Results	1206
Atrial Fibrillation	1206
Atrial Flutter	1213

CHAPTER	PAGE
<i>Paroxysmal Auricular Tachycardia</i>	1215
<i>Extrasystoles</i>	1217
<i>Nodal Tachycardia</i>	1218
<i>Ventricular Tachycardia</i>	1219
Reasons for Failure	1222
Toxic Symptoms	1222
Accidents and Sudden Deaths	1221
Summary	1226
XL Total Thyroidectomy in the Treatment of Chronic Heart Disease	1230
Physiology	1230
Results	1232
Comparison with Results Obtained by Other Methods of Treatment	1235
Technic	1238
Selection of Cases	1239
Preoperative Preparation	1240
Operative Technic	1240
Postoperative Management and Supervision	1242
Summary	1243
Illustrative Cases	1244
XLI Heart and Deficiency Diseases	1252
General Considerations	1252
General Undernutrition and Inanition	1254
Water and Salt Deficiency	1256
Deficiency of Certain Nutritional Factors in Pernicious Anemia	1257
Beriberi	1259
Electrocardiographic Changes	1263
Hemodynamics of the Circulation	1263
Chemical Changes	1264
Morphological Changes	1264
Pathogenesis	1264
The Role of Alcohol	1265
Differential Diagnosis	1266
Organic Heart Disease and Beriberi	1267
Treatment	1268
Illustrative Cases	1270
Scurvy	1291
XLII Physical Therapy in Cardiovascular Disease	1294
Introduction	1294
The Various Forms of Physical Therapy	1297
Rest	1297
Exercise	1297
The Schott Exercises	1299
Passive Exercise	1300
Mechanotherapy	1301
Massage	1301
Hydrotherapy	1301
Pulse	1308
Blood Pressure	1308
Venous Circulation	1309
The Skin Capillaries	1309
The Minute Volume Output of the Heart	1309
Effect Upon Respiration	1310
Respiratory Metabolism	1310
Influence on Skin Physiology	1311
Summary	1311
Results of Treatment	1312

TABLE OF CONTENTS

vi

CHAPTER

PAGE

Occupational Therapy	1314
Etiology of Cardiovascular Disease and Indications for Physical Therapy	1315
Congenital Cardiovascular Defects	1315
Rheumatic Heart Disease	1316
Acute and Subacute Bacterial Endocarditis	1316
Cardiovascular Syphilis	1316
Other Infections (Scarlet Fever, Diphtheria)	1316
Thyrotoxic Cardiovascular Disease	1316
The Myxedematous Heart	1317
Heart and Deficiency Disease (The Beriberi Heart)	1317
Degenerative Heart Disease Including Hypertensive Heart Disease	
Coronary Artery Disease and Coronary Thrombosis	1317
Pulmonary Heart Disease	1318
Neurocirculatory Asthenia and the Cardiac Neuroses	1318
Sources Available for Administration of Physical Therapy	1318
VIII Normal Blood Pressure and Its Physiologic Variations	1320
Introduction	1320
Standardization of Blood Pressure Determinations	1322
Blood Pressure Equipment	1322
The Patient	1322
Position and Method of Application of the Cuff	1323
Significance of Palpatory and Auscultatory Levels	1323
Position and Method of Application of Sphygmoscope	1323
Determination of the Systolic Pressure	1323
Determination of the Diastolic Pressure and the Pulse Pressure	1323
Explanatory Comments	1321
Physiologic Variations of Normal Blood Pressure	1329
Posture	1329
Sleep	1330
Diurnal Variations	1330
Emotions	1331
Muscular Effort	1333
Meals	1333
Difference in Blood Pressure in the Two Arms	1333
Position of the Arm	1334
Menstruation and Pregnancy	1334
Constipation	1334
Alcohol	1334
Tobacco	1334
Weight	1335
Body Build	1335
Height and Surface Area	1336
Climate and Temperature	1336
Barometric Pressure	1337
Comment	1337
Cold Pressor Test	1338
Normal (Normal Blood Pressure)	1338
Normal Hyperreactive (Blood Pressure Within Normal Limits)	1338
Essential Hypertension	1339
Normal Blood Pressure	1339
Discordance in Results Reported by Different Observers	1339
Desirability of Using the Mode and Not the Mean	1340
Influence of Age	1341
Range of Normal	1345
Sex	1345
Conclusions	1346

CHAPTER	PAGE
XLIV Capillary Circulation	1350
Clinical Importance	1350
Anatomy and Physiology	1350
Nervous Regulation Central and Local	1352
Local Regulation by Substances Formed in the Tissues	1352
Hormone Regulation	1353
Methods of Clinical Study	1353
Visualization	1354
Capillary Pressure	1355
Capillary Fragility	1360
Capillary Permeability	1361
Capillaries in Disease	1361
XLV Venous Pressure	1367
Indirect Method	1368
Direct Method	1369
Venous Pressure Under Normal Conditions	1371
Relation Between Venous Pressure and Cerebrospinal Fluid Pressure	1372
Relation Between Venous and Arterial Pressure	1373
Cardiac Insufficiency	1376
Venesection	1377
XLVI Shock	1381
Introduction	1381
Definition	1382
Is There Always a Diminished Blood Volume in Shock	1382
Is the Loss of Circulating Blood Volume Progressive	1382
Is There Tissue Anoxia in Shock	1383
Is There Reduced Circulation in Shock	1381
Clinical Picture	1384
Pathology	1386
Physiology	1387
Cardiovascular	1387
Gastrointestinal	1388
Genitourinary	1389
Neuromuscular	1389
Respiration	1390
Chemistry	1391
Etiology	1393
Prognosis	1397
Treatment	1398
Conclusions	1410
XLVII Hypertensive Arterial Disease	1413
Introduction	1413
Incidence	1413
Mortality and Causes of Death	1411
Disability	1411
Symptoms	1415
Diagnosis	1416
Pathologic Physiology	1417
Peripheral Resistance	1418
Control of Arteriolar Tone	1420
Results of Arteriolar Constriction	1420
Etiology Pathogenesis and Pathology of Hypertensive Arterial Disease	1421
Etiology	1422
Pathogenesis	1427
Stages of Hypertensive Disease	1432
Pathology	1433
Consequences of Hypertension	1434

TABLE OF CONTENTS

xi

CHAPTER	PAGE
Cardiac Symptoms	1436
Neurologic Consequences	1438
Renal Consequences	1443
Prognosis	1448
Treatment of Hypertensive Disease	1453
Therapy Directed Against Etiology	1454
Diet	1457
Fluid Intake	1458
Tobacco Alcohol and Coffee	1458
Psychogenic Factors	1459
Therapy to Reduce the Burden of Injured Structures	1459
Psychological Measures	1460
Medicinal Measures	1461
Physical Measures	1465
Surgical Measures	1466
Aid to Tissue Nutrition and Respiration	1467
Summary	1470
XVIII <i>Psychic Factors in Essential Arterial Hypertension</i>	1474
Methods of Approach to the Problem	1474
Methods of Study	1475
The Time Element	1480
Social Climate and Attitude	1482
Diet	1485
Habit and Emotional Attitude	1486
What Does Psychogenic Mean	1486
Emotional Relations	1489
A Plan of Procedure	1493
XIX <i>Low Arterial Pressure</i>	1498
Historical	1498
Present Status	1498
Definition	1499
Physiological Considerations	1500
Adaptability of Forces in the Circulation	1500
The Energy Index	1501
Etiology	1504
Incidence	1504
In Health	1504
In Disease	1506
Clinical Grouping of Cases	1506
Symptoms	1507
Low Arterial Pressure From the Standpoint of the Human Constitution	1511
Anatomical and Pathoanatomical Panel	1511
Physiological and Pathophysiological Panel	1511
Immunological Pathoimmunological Panel	1527
Theories Concerning Causation of Low Arterial Pressure	1531
Glucose—The Fuel of Life	1532
Prognosis	1533
Treatment	1536
General Treatment	1537
L <i>Arteriosclerosis</i>	1541
Introduction	1541
Pathology	1541
Pathogenesis	1543
Incidence	1544
Localization of Arteriosclerosis	1545
Etiology	1547
Phlebosclerosis	1550

CHAPTER	PAGE
Sclerosis of Capillaries	1552
"Primary Arteriosclerosis	1552
Experimental Arteriosclerosis	1553
Relation of Infections Food Products of Metabolism Poisons Etc to Arteriosclerosis	1556
Clinical Importance of Arteriosclerosis of the Greater Circulation	1556
Arteriosclerosis Associated with Diabetes	1557
Monckeberg Arteriosclerosis	1557
Pseudo or Transient Arteriosclerosis	1558
Relation of Race to Arteriosclerosis	1558
Relation of Heredity to Arteriosclerosis	1559
Diagnosis of Arteriosclerosis	1561
Prophylaxis	1562
Treatment	1562
Educational	1562
Exercise and Rest	1563
Diet	1561
Drugs	1561
LI Periarthritis Nodosa	1564
Synonyms	1564
Definition	1564
Review of Literature	1568
Etiology	1569
Pathology	1568
Symptoms	1571
Diagnosis	1571
Prognosis	1571
Treatment	1573
LII Thromboangitis Obliterans	1579
Clinical Concept	1579
Clinicopathological Acceptation	1580
Pathological Concept	1582
Other Theories of Pathogenesis	1583
Enigma of Vascular Disease	1585
Clinical Amplification	1591
Universality of Lessons of T A O	1591
Equivocalness of Observational Information	1601
Clinical Capriciousness	1601
Classificatory Objectives	1602
Distinguishing Typifying Peculiarities	1603
LIIL Erythromalgia (Erythromelalgia) of the Extremities	1605
Definition	1605
Pathologic Physiology	1606
Increased Temperature of the Skin	1606
Vasodilation	1607
Hydrostatic Pressure	1607
Susceptible State of the Skin	1608
Vasoconstriction	1608
Nature of the Distress	1608
Diagnosis	1609
Methods of Study	1609
Report of Cases	1610
Treatment	1613
IIIV Lymphedema of the Extremities	1616
Etiology	1616
Noninflammatory Lymphedema	1617
Primary Lymphedema	1617

	Congenital Lymphedema	1618
	Secondary Lymphedema	1619
	Inflammatory Lymphedema	1620
	General Characteristics	1620
	Primary Lymphedema	1621
	Secondary Lymphedema	1621
	Differential Diagnosis	1621
	Medical Treatment	1626
	Control of Edema	1626
	Treatment and Prevention of Inflammation	1627
	Surgical Treatment	1628
LV	Sudden Embolism and Thrombosis of Arteries of the Extremities	1632
	Etiology	1632
	Symptoms	1636
	Interpretation of Symptoms	1638
	Diagnosis	1641
	The Course of Events in Sudden Arterial Occlusion	1643
	Pathologic Changes Following Embolism	1645
	Prognosis	1645
	Treatment	1647
LVI	Thrombophlebitis	1651
	Etiology	1651
	Local	1652
	Hematogenic Thrombophlebitis	1653
	Secondary (Complicating) Thrombophlebitis	1654
	Primary Thrombophlebitis	1656
	Pathology	1657
	Pathologic Physiology	1659
	Clinical Symptoms and Signs	1661
	Complications and Sequelae	1665
	Diagnosis	1666
	Treatment	1667
	Local Thrombophlebitis	1667
	Hematogenic Thrombophlebitis	1668
	Secondary Thrombophlebitis	1668
	Primary Thrombophlebitis	1673
	Postphlebitic Neurosis	1673
	Chronic Venous Insufficiency	1674
LVII	Acquired Arteriovenous Fistula Temporal Arteritis and Aneurysm	1676
	Acquired Arteriovenous Fistula	1676
	Definition	1676
	<i>Etiology and Physiology</i>	1676
	Diagnosis	1677
	Treatment	1679
	Temporal Arteritis	1681
	Etiology	1681
	Pathology	1682
	Diagnosis and Prognosis	1682
	Differential Diagnosis	1684
	Treatment	1684
	Aneurysm	1685
	General Considerations	1685
	Etiology	1685
	Pathologic Characteristics	1686
	Signs and Symptoms	1686
	Treatment	1689

CHAPTER	PAGE
VIII Arteriosclerosis Obliterans	1691
Etiology	1691
Age	1691
Race and Climate	1691
Nutrition	1691
Infections Acute and Chronic	1699
Hereditary	1699
Worry Exercise Hard Work	1700
Lead	1700
Manganese	1700
Signs and Symptoms of Arteriosclerosis Obliterans As It Affects the Extremities	1700
Findings by Means of Special Examinations	170
Surface Temperature Studies	1706
Reflex Vasodilation Tests	1706
X rays—Flat Plates	1707
Arteriography	1707
Histamine Flare Tests	1708
Measured Work Tests	1709
Pathology and Pathogenesis	1709
Mönckeberg's Sclerous	1710
Recent Studies	1711
True and False Aneurysms in the Peripheral Arteries	1712
Treatment	1713
Rest	1713
Position	1713
Exercise	1711
Tobacco	1711
Alcohol	1711
Baths	1716
Tissue Extract	1718
Pressure Suction Boot Treatment	1719
The Use of the Sanders Oscillating Bed	1721
Intermittent Venous Hyperemia	1722
Saline and Other Solutions Intravenously	1722
Vasodilating Drugs	1723
The Use of Antiseptics in Arteriosclerosis	1724
Surgical Aspects of Arteriosclerosis	1724
Amputation	1725
IX Raynaud's Syndrome and Acrocyanosis	1729
Raynaud's Syndrome	1729
Definition	1729
Pathology and Pathological Physiology	1729
Etiology	1731
Cold	1731
Emotion	1732
Repeated Vibration or Percussion Stimuli	1732
Occlusive Arterial Disease	1733
Arsenic	1733
Disturbed Calcium Metabolism	1733
Sex Hormones	1734
Signs Symptoms and Course	1734

	Free Raynaud's Syndrome (Early Raynaud's Syndrome)	1733
	Trophic Changes	1735
	Scleroderma (Sclerodactylia Acrosclerosis)	1735
	Gangrene	1736
	Treatment	1736
	Protection	1736
	Treatment of Local Conditions	1737
	Mecholyl Iontophoresis	1737
	Vasodilating Drugs	1739
	Tobacco	1739
	Surgery of Raynaud's Disease	1740
	Acrocyanosis	1741
	Signs and Symptoms	1741
	Etiology	1743
	Cold	1743
	Mental Disease	1743
	Activity	1743
	Endocrine Relationships	1743
	The Relationship to the Autonomic Nervous System	1744
	Avitaminosis	1744
	Physiological Pathology	1741
	Treatment	1746
LX	Vascular Anomalies	1748
	Introduction	1748
	Simple Angioma	1750
	Port wine Stain	1751
	Cavernous Angioma	1753
	Cirsoid Aneurysm	1753
	Congenital Arteriovenous Aneurysm	1754
	Treatment	1756
LXI	Varicose Veins	1770
	Introduction	1770
	Etiology	1770
	Symptoms and Diagnosis	1777
	Test of Venous Circulation in the Varicose Extremity	1778
	Complications of Varicose Veins	1789
	Treatment of Varicose Veins and Complications	1786
LXII	Pathogenesis and Treatment of Edema	1796
	Introduction	1796
	Factors Concerned in the Normal Distribution of Body Fluids	1797
	Factors in the Pathogenesis of Edema	1800
	Capillary Pressure	1801
	Hypoproteinemia and Reduced Colloid Osmotic Pressure of the Blood Plasma	1802
	Permeability of the Capillary Wall	1803
	Lymphatic Drainage	1805
	Tissue Pressure	1805
	Sodium Chloride Intake	1806
	Fluid Intake	1807
	Heat	1807
	Disturbed Innervation	1807
	Custom Less Well defined Factors	1808

CHAPTER

PAGE

Summary	1809
Treatment	1810
General Measures	1810
Diuretic Drugs	1813
Additional Measures Used in Treating Nephritic Edema	1816
Additional Measures Used in Cardiac Edema	1817
Excessive Elimination of Water	1818
Clinical Examples	1819
Nephritic Edema	1819
Nephrotic Edema	1820
Cardiac Edema	1822

LIST OF ILLUSTRATIONS, VOLUME II

	PAGE
Adrenalin effect of intravenous injection of on blood pressure plasma volume and blood flow, chart	1406
Alex Cappelen who performed the first operation upon the human heart	1446
Anomalous blood vessel pathological specimen	1764
Anomalous lymph channel and degenerated nerve plexuses of left leg	1766
Arteriogram showing fistula between femoral artery and vein	1680
Arteriosclerosis obliterans arteriographic study in which femoral artery was obliterated in mid thigh but collateral branches carry blood around of situation and back into femoral artery above popliteal space	1695
Arteriosclerosis obliterans arteriographic study showing false aneurysm in popliteal space	1696
Arteriosclerosis obliterans atheroma of a peripheral nerve	1692
Arteriosclerosis obliterans cross section of a peripheral artery showing some thickening of intima	1692
Arteriosclerosis obliterans cross section of a peripheral artery showing thickening of intima with almost complete obliteration of lumen	1692
Arteriosclerosis obliterans intima and intermediary layers have been destroyed and replaced by calcification	1692
Arteriosclerosis obliterans scattered plaques of calcification along course of femoral artery in thigh	1695
Arteriosclerosis obliterans x ray of foot showing definite evidence of arteriosclerosis of posterior tibial artery with no change in dorsalis pedis	1691
Arteriosclerosis obliterans x ray of leg and foot showing definite evidence of arteriosclerosis of posterior tibial and dorsalis pedis arteries	1693
Arteriosclerotic ulcer iatrogenic ulcer and traumatic ulcer	1791
Arteriovenous aneurysm congenital	1755
Arteriovenous fistula and port wine stains	1763
Arteriovenous fistula congenital	1760
Arteriovenous fistula heart before and after operation	1678
Arteriovenous fistula of hand	1758
Arteriovenous fistula of hand sketch showing operation	1759
AV dissociation and AV rhythm auricular flutter	1136
AV heart block ventricular extrasystoles and ventricular paroxysmal tachycardia caused by digitalis	1138
Blood flow in normal control chart	1383
Blood flow in surgical shock chart	1391
Blood pressure in poor sleep chart	1521
Blood sugar and blood pressure chart	1517
Camera lucida outline of vascular pattern of small blood vessels in the frog	1351
Capillaries of nail fold photomicrograph	1351
Capillary pressure by microinjection diagram of apparatus for	1355
Carbon dioxide bubbles collecting on skin demonstration of	1301
Carbon dioxide mineral bath	1206
Cardiac bedstead (Lewis) with back rest in position	1069
Cardiac bedstead (Lewis) with back rest thigh rest and lowered leg rest—converting the bed into a chair	1069
Cardiac contusion with fractures from being butted by a bull	1157
Cardiac dilatation acute and congestive failure associated with polyneuropathy cardiac x ray shadow before treatment	1289
Cardiac dilatation acute and congestive failure associated with polyneuropathy cardiac x ray shadow following improvement	1290

	PAGE
Cardiac pains composite picture of diagrams	1510
Cardiac patient engaged in machine sewing and fine hand sewing	1056
Cardiac patient engaged in woodworking	1058
Cardiacs in industry	1055
Cardiac x ray shadow in a case of severe congestive failure of circulation mild pellagra and polyneuritis and fatal circulatory collapse	1269
Cardiosensory pathways diagrammatic representation of	1187
Circulation diagram of showing short circuit of blood through patent ductus arteriosus	1171
Compression of heart by scar before and after operation	1169
Compression of heart due to scar kymograph roentgenogram	1152
Congestive failure of circulation and polyneuritis clinical chart	1279
Congestive failure of circulation and polyneuritis electrocardiograms	1280
Congestive failure of circulation cardiac asthma and polyneuritis electrocardiograms	1287
Congestive failure of circulation cardiac x ray shadow	1275
Congestive failure of circulation cardiac x ray shadow after treatment	1277
Congestive failure of circulation clinical chart	1276
Congestive failure of circulation electrocardiograms	1271
Congestive failure of circulation the only manifestation of vitamin deficiency cardiac x ray shadow after improvement	1286
Congestive failure of circulation the only manifestation of vitamin deficiency cardiac x ray shadow before vitamin B ₁ treatment	1283
Congestive failure of circulation the only manifestation of vitamin deficiency clinical chart	1281
Congestive failure of circulation the only manifestation of vitamin deficiency electrocardiograms	1282
Contusion of heart and rupture of diaphragm from being run over by automobile diagram	1159
Deaths from all causes and from diabetes chart	1530
Diagram illustrating filtration and absorption in relation to capillary blood pressure and the colloid osmotic pressure of the plasma proteins	1799
Diagram of possible etiology of hypotension	1533
Digitalis effects of on electrocardiogram	1141
Digitalization stage at which it will preserve the optimum cardiac output	1003
Direct manometer for measuring venous pressure in terms of centimeters of blood	1570
Direct method of Moritz and von Tabora of determining venous pressure	1569
Edema nephrotic chart illustrating clinical course and therapy	1821
Embolism arterial probable course of events in diagrams	1633
Foreign body penetrating heart from esophagus	1166
Graphic representation of six pulse beats each beat consisting of a force of 200 mm Hg	1562
Heart torn from great vessels by impact of fall	1156
Hemangioma	1756
Hemangioma cavernous	1751
Hemangioma hypertrophic	1750
Hemangioma of face diagrams showing excision	1757
Hemihypertrophy involving right upper and lower extremities scapula and pelvic girdle	1707
Hemorrhage effect of on blood pressure and blood flow of a dog which had recovered after bilateral thoracolumbar ganglionectomy chart	1596
Hemorrhage effect of on blood pressure and blood flow of a normal unanesthetized dog chart	1597
Home education of a cardiac case	1019
Home education of a cardiac case	1051
Hypertrophic degeneration of muscle fibers photomicrograph	1270
Hyperkeratosis at site of previous varicose ulceration	1776
Hypersthenic type	1512
Hypertension and anemia course of over two years chart	1163
Hypertension course of under bismit subnitrate therapy chart	1161
Hypertensive arterial disease diagram of pathogenesis	1129

	PAGE
Hypotension in hyposthenic type	1512
Hypotension in sthenic type	1512
Indirect venous pressure manometer	1368
Injury to heart from being kicked by colt	1160
Internal saphenous vein close to saphenofemoral junction	1773
Intraarterial visualization of brachial artery and main branches by skiodan	1761
Microscopic appearance of duodenum of dog in which shock had been produced	1387
Microscopic appearance of liver of dog in which shock had been produced	1389
Muscular tension in sleep chart	1521
Paravertebral injection of thoracic sympathetic ganglia	1189
Paravertebral injection of thoracic sympathetic ganglia	1189
Periarteritis nodosa enlarged view of photomicrograph of longitudinal section through a branch of mesenteric artery	1575
Periarteritis nodosa of coronary artery photomicrograph	1572
Periarteritis nodosa of liver	1570
Periarteritis nodosa of mitral leaflet photomicrograph	1571
Periarteritis nodosa of mitral valve	1569
Periarteritis nodosa photomicrograph of longitudinal section through a branch of mesenteric artery	1575
Periarteritis nodosa photomicrograph of section of nodule in diaphragm	1573
Periarteritis nodosa photomicrograph of typical lesion	1569
Perivascular edema and separation of muscle fibers photomicrograph	1271
Perthes test	1781
Port wine stain and multiple capillary angiomas	1761
Port wine stain limited to left half of lower extremity trunk and face	1752
Pulse pressure chart showing maximum and minimum in the erect and horizontal positions	1521
Pulse pressure chart showing maximum and minimum in the erect and horizontal positions	1522
Pulse pressure chart showing rapid fall	1523
Raynaud's disease beginning erythema ten minutes after return to warm environment color plate	faciug 1732
Raynaud's syndrome showing extreme pallor and moderate cyanosis associated with vaso spasm produced by cold color plate	faciug 1730
Rupture of right auricle from cive in accident diagram	1161
Salt free diet effects on blood pressure and urinary chlorides chart	1518
Saphenous vein at saphenofemoral junction tributaries of diagram	1789
Saratoga Sp1 aerial view of	1295
Saratoga Springs Island Spouter with its interesting mineral deposits	1296
Scotch douche	1305
Section of wall of vein one week after injection with 50 per cent dextrose	1791
Shock process of diagram	1382
Shock treatment of	1109
Stab wound of heart suture of	1151
Steering wheel accident to heart	1158
Strax and DeGriff apparatus for determining capillary pressure	139
Systolic blood pressure in diabetes chart	1529
Tachyarradia simple and associated A V block caused by digitalis	1135
Thrombophlebitis acute iliofemoral frame for elevation of leg in treatment of	1669
Thrombophlebitis acute iliofemoral complicating chronic ulcerative colitis infrared photograph	1661
Thrombophlebitis iliofemoral heavy pure rubber bandage applied over white cotton stocking in treatment of	1672
Thrombophlebitis iliofemoral untreated acute stage infrared photograph	1663
Thrombophlebitis of inferior vena cava dilated tortuous superficial abdominal and thoracic veins in old case of	1660
Thrombophlebitis of long saphenous vein	1662

	PAGE
Thrombophlebitis primary involving superficial veins of inner side of foot	1661
Thrombus in right ventricle	1163
Thyroidectomy total results following chart	1233
Thyroidectomy total results following in angina pectoris chart	1234
Thyroidectomy total results following in congestive failure chart	1234
Thyroidectomy total results following in paroxysmal dyspnea chart	1235
Trendelenburg test	1779
Triad for acute compression of heart diagram	1120
Triad for chronic compression of heart diagram	1151
True cardiac pain areas diagrams	1509
T waves changes in brought about by digitalis	1132
Ulceration with ringworm infection and psoriasis tuberculous ulcer elephantiasis with small ulceration and neglected thrombophlebotic ulcer with lymphostasis	1782
Valvular mechanism of veins of lower extremities diagram	1787
Varicose ulcer	1783
Varicose ulcers healed of leg	1775
Varicose veins blowout at lower third of thigh	1780
Varicose veins of leg	1774
Vascular anomaly congenital	1777
Vascular mass localized in popliteal fossa	1762
Venous valvular insufficiency with opening of subcapillary venous plexuses	1771

CHAPTER XXXI

THE CLINICAL EFFICACY OF VARIOUS DIGITALIS PREPARATIONS

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Although the indications and methods of administration of digitalis are discussed in considerable detail in Chapter XXXIV, yet, since there still exists confusion in the mind of the average practitioner as to the indications for the use of digitalis, the best method of administration and the most efficient type of preparation to be used, we have prepared this chapter in an attempt to clarify this point. Unfortunately, from time to time various articles with conflicting opinions as to the indications and contraindications for digitalis have appeared in the medical periodicals. Furthermore, the problem has been rendered more difficult by the more or less generalized change from the tincture to use of the powdered leaves in tablet, capsule or pill form, the introduction of the term cat unit* in expressing biologic potency and dose and the pressure of salesmanship of the manufacturing drug firms as to the special merits of their respective preparations.

The purpose of the present paper is (1) to emphasize a few of the main indications and contraindications for digitalis, (2) to review briefly its mode of action, the dose and methods of administration, and (3) to discuss the therapeutic merit of several special preparations of the isolated digitalis principles (glycosides), compared with whole leaf preparations, as determined in a clinical study during the last eight years.

INDICATIONS

More than 100 years ago digitalis lost favor as a therapeutic agent because of its inability to slow tachycardias due to fever, and yet today many physicians prescribe digitalis with the hope of slowing rapid heart action due to fever, thyrotoxicosis, hypersensitivity of the sympathetic nervous system and peripheral circulatory failure. This practice is espe

* A cat unit represents the minimum amount of digitalis which is required per kilogram of body weight to kill a cat when injected slowly and continuously intravenously. It represents 0.1 Gm. (1½ grains) of powdered leaves or 1 cc. (15 minims) of tincture.

cially common in connection with surgical procedures digitalis being given postoperatively in some places almost as a matter of routine

Needless to say digitalis proves of no advantage in the treatment of such conditions except in certain cases of thyrotoxicosis accompanied by cardiac disease of different etiology (such as a rheumatic valvular defect associated with congestive heart failure) or in cases of pneumonia complicated with auricular fibrillation or auricular flutter. As shown in the study of pneumonia at Bellevue Hospital¹ digitalis when indicated in the treatment of this disease should be given only in divided doses since massive doses may prove distinctly dangerous.

During the last two decades several investigators² have called attention to the differential diagnosis between circulatory failure due to disease of the heart and circulatory failure resulting from collapse of the peripheral vascular system. As described by Harrison³ The clinical picture of peripheral circulatory failure (shock, collapse) is characterized by weakness as the chief subjective phenomenon and by ashen pallor, cold clammy skin, tachycardia, weakness of the pulse, diminution in systolic pressure. In emergencies of this character digitalis proves of but little—if any—benefit and through recognition of this fact the formerly rather prevalent procedure of administering this drug postoperatively (in ridiculously small doses) to patients with circulatory failure of peripheral origin has been abandoned. Digitalis is seldom indicated in emergencies unless there is definite evidence of right or left ventricular failure and then in order to secure clinical benefit within a few hours large doses are necessary.

Although some clinicians still question the statement that proper digitalization improves tonicity and contractility of the myocardium it is our opinion as stated in a previous publication by one of us⁴ that the therapeutic benefit of digitalis is effected in one or all of three ways as follows:

- 1 By slowing the heart rate that is by lessening the number of ventricular systoles per minute the diastolic period is lengthened whereby ventricular filling is rendered more complete and the heart muscle fibers are afforded more rest and as a consequence there may result a greater expulsion of blood into the circulation with each systole.

- 2 By increasing the cardiac tone thereby relieving or preventing dilatation of the heart chambers beyond the physiologic limit the opti

imum cardiac output is made possible. When the length of the heart muscle fibers is increased beyond a certain limit the cardiac output is decreased and heart failure is believed to result. Restoration of the fibers to a shorter length is a factor in bringing about an increase in cardiac output with the possible return of circulatory efficiency.

3 Through increase of the extent of ventricular contraction there tends to be an increase in cardiac output when heart failure is present.



FIGURE 1 Stage at which digitalization will preserve the optimum cardiac output

If the effects mentioned are to be expected from digitalization the question arises as to when in the course of progressive cardiovascular disease the patient should be digitalized. Christman⁵ expressed the opinion that as soon as a diagnosis has been made of cardiovascular disease (particularly hypertension or valvular disease) which may place an additional burden on the myocardium the patient should be digitalized and digitalization should be maintained throughout the remainder of life. On the other hand Harrison and Leonard⁶ (in a study of dogs) and

Burwell Neighbors and Regen⁷ (in a study of human beings) found that a reduction in output of the normal heart occurs with full digitalization. Certain studies⁸ suggest that if the heart is normal or has perhaps a slight degree of dilatation and hypertrophy digitalis lessens the efficiency of the heart muscle and also decreases the flow in the coronary arteries. The same studies indicate that there may be a stage in the progressive dilatation and hypertrophy of a laboring myocardium at which digitalis seems to improve the efficiency of the heart muscle and also the flow from the coronary sinus into the heart. Hypertrophy and dilatation unchecked tend toward a point where a certain optimal length of the fibers of the heart muscle is exceeded and a decrease in cardiac output results (described by Starling⁹ as the law of the heart), with gradual or sudden development of signs of heart failure. On the basis of this hypothesis it is the physician's responsibility to estimate—through the patient's history, the physical appearances, electrocardiographic and x-ray studies and his knowledge of the usual progression of the various cardiovascular diseases—just when the stage has been reached (as shown in the accompanying illustration) at which digitalization will preserve optimum cardiac output through increase of tonicity and extent of ventricular contraction.¹⁰

It is our belief therefore that in the treatment of patients with progressive chronic cardiovascular disease digitalization should not be started as a matter of routine at the time of diagnosis but when in the opinion of the physician the pathological processes have progressed to a point where digitalization may increase ventricular output and improve coronary flow.

METHOD OF ADMINISTRATION

The vast majority of patients can take digitalis by mouth. The emetic action of digitalis is not due to a direct irritant action on the gastric mucosa but is a reflex effect from the direct action of the drug on the heart (the impulses passing from the heart to the vomiting center in the medulla). * Occasionally psychic vomiting due to knowledge of the toxic gastric effects is encountered. Intravenous digitalis therapy is seldom indicated. Subcutaneous administration is necessary only in the

* It cannot be too strongly emphasized that the nausea and vomiting of digitalis intoxication is a brain center effect and not due to its effect on the stomach. The common experiment of giving a cat a toxic dose of digitalis intravenously so that the cat proceeds to vomit is an excellent illustration.

presence of vomiting or unconsciousness or when the patient is unable to swallow. Rectal administration is seldom necessary.

It is generally admitted by physicians with experience in both methods of administration that tablets, capsules or pills of powdered digitalis leaves are much more practical than the tincture. In the first place, such preparations seem to maintain their potency better than the tincture and, in the second place, the dosage is much more accurate, since even with the standard minim dropper the patient is apt to miscount the number of drops. The impossibility of accurate dosage in the absence of a standard minim dropper is well known to all who have tested the average medicine dropper supplied by the drug store*. Furthermore it is more convenient to carry tablets, capsules or pills than a bottle of the tincture.

According to our experience the large dose method of administering digitalis is seldom necessary. In emergency cases when there is no vomiting, full digitalization can be accomplished with tablets of standardized digitalis (or their equivalent in glucoside preparations) when given by mouth, in from 0.3 to 0.4 Gm. ($4\frac{1}{2}$ to 6 grains) doses every six hours within 24 to 36 hours. In the average case of congestive heart failure complete digitalization can be accomplished in from 48 to 72 hours by administration of 0.2 Gm. (3 grains) of digitalis three times a day. For an ambulatory patient with heart failure of mild or moderate degree full digitalization can be accomplished in six or seven days by 0.1 Gm. ($1\frac{1}{2}$ grains) tablet given twice a day. After digitalization it has been our experience that the average maintenance dose is about 0.1 Gm. daily. Of course, some patients may require slightly larger doses, while in other instances the maximum effect is maintained by means of considerably small doses, even as little as 0.03 Gm. ($\frac{1}{2}$ grain) daily.

In summary, then, 0.1 Gm. of a properly standardized tablet, capsule or pill of digitalis leaves is equivalent to 1 cc. (15 minims), or approximately 45 drops, of a well standardized tincture. In general, physicians are finding the tablet, capsule or pill a much more convenient form for administering digitalis than the old fashioned tincture. It is necessary to use between 1 and 2 Gm. (15 and 30 grains) of digitalis to digitalize fully the average adult patient. Except in emergencies our usual routine

* A dose in drops from an ordinary dropper has from two to three times the number of drops as the same amount measured in minims.

TABLE I
CLINICAL COURSE OF PATIENT S F

Date	6/10*	7/13	8/3*	8/17	9/21	12/13
Aver daily dose grains	1½	0	1/160	1/240	1/240	1/240
Weight pounds	118	116	116	115	116½	118
Ventricular rate	80	100	116	70	72	84
Pulse rate	80	92	88	70	72	84
Dyspnea	0	0	+	0	0	0
Edema	0	0	0	0	0	0
Lung (rales)	0	0	+	0	0	0
Liver cm palp	0	0	0	0	0	0
Blood pressure	110/70	110/76	88/45	106/70	106/64	120/85
Vital capacity cc	2670	2070	2150	2670	2600	2600

Date	1/10‡	6/21§	7/7	10/4	1/31	4/11
Aver daily dose grain	1/240	1/320	1/670	1/600	1/600	1/600
Weight pounds	118	121	116	122	122	124
Ventricular rate	66	112	68	80	68	80
Pulse rate	66	100	68	80	68	90
Dyspnea	0	+	0	0	0	0
Edema	0	0	0	0	0	0
Lungs (rales)	0	+	0	0	0	0
Liver cm palp	0	0	0	0	0	0
Blood pressure	110/70	104/78	110/70	104/70	116/70	120/89
Vital capacity cc	2400	2000	2150	2150	2100	2000

Date	7/11*	8/8*	8/22	9/19	10/10
Aver daily dose grain	1/600		1/240	1/240	1/240
Weight pounds	126	129	130	129	132
Ventricular rate	84	72	112	76	76
Pulse rate	84	72	96	76	76
Dyspnea	0	0	+	0	0
Edema	0	0	0	0	0
Lungs (rales)	0	0	+	0	0
Liver cm palp	0	0	0	0	0
Blood pressure	114/80	120/80	120/90	120/70	104/76
Vital capacity cc	1900	1700	1250	1500	1750

* This patient was observed from January to October while receiving Burroughs Well come and Company digitalis 1½ grains daily. From the following October to June his condition was controlled by 1½ grains of digitalis daily. All medication was stopped on this date.

† Administration of Verodigen 1/200 grain daily started on this date.

‡ Condition previously controlled by this dose of verodigen for nine months. All medication stopped on this date.

§ Digitaline (Nativelle) started on this date.

|| Maintenance dose of 1/60 grain of digitaline (Nativelle) for 13 months prior to this date.

* All medication stopped on this date.

‡ Digoxin 1/40 grain twice daily started on this date.

is to give the patient 0.1 Gm of powdered digitalis four times a day (0.39 Gm—6 grains daily) for three days. Thus with a total of 1.166 Gm (18 grains) we approach full digitalization with little danger of toxic symptoms. From then on the daily dose is determined by the condition of the patient's circulation or the development of toxic symptoms. The average daily maintenance dose of digitalis is between 0.03 and 0.19 Gm ($\frac{1}{2}$ and 3 grains) a day.

CHOICE OF PREPARATION

The proof or disproof of a drug's efficacy rests finally on the test in patients. This statement of Sir Thomas Lewis applies especially to digitalis preparations. A drug of the value and having the widespread use of digitalis deserves the greatest consideration from the practical clinical standpoint. In a given case the therapeutic efficiency may largely depend on a sufficient but nontoxic dose. The present popularity of preparations made from powdered whole digitalis leaves has logically evolved from the stability, accuracy of dosage and satisfactory clinical results of this form of the drug. In addition to whole leaf products many purified preparations containing one or more of the glucosides of digitalis are now available. It is possible that the necessity for bio-assay may be obviated with these preparations and clinically they should be reliable and efficient. The great variation in their equivalent doses however has added confusion to the problem of digitalizing the patient and establishing a maintenance dose.

The clinical comparison of different preparations of digitalis is a difficult procedure. The digitalizing dose and the daily maintenance dose of one preparation may be sufficient to maintain circulatory efficiency in a given patient while the same dose of another preparation may while satisfactory hold the patient continuously closer to toxic manifestations. In other words, in making such a study it must be remembered that there exists in a majority of patients with established auricular fibrillation a fairly wide margin between the minimum dosage necessary for optimum digitalization and the maximum dosage which can be tolerated without the incidence of toxic effects.¹¹

During the past eight years we have conducted a clinical study using several preparations of digitalis.¹² The data on 56 of a large number of patients observed during this period are satisfactory for analysis. Thirty of the patients had organic heart disease with chronic auricular

fibrillation and were taking digitalis when they came under observation. All these patients were observed for two or more years and were ambulatory, and practically all developed rapid ventricular rates with pulse deficit if digitalis was omitted. Seventeen were observed for three or more years and 11 for over four years. Twenty six patients had never received a preparation of digitalis before coming under observation because of heart failure. All were hospitalized, and the digitalizing dose of a given preparation was determined by clinical trial. Seventeen patients had auricular fibrillation, three had auricular flutter and in six normal sinus rhythm was present.

Our first study was with American Heart Association whole leaf tablets of digitalis as prepared by Gold at Cornell University, the tabloids of whole leaf digitalis prepared by Burroughs Wellcome and Company and Digalen a preparation of purified glucosides supplied by Hoffman LaRoche Inc. Ambulatory patients with established auricular fibrillation, 25 in number, were selected from the adult heart clinic of the Pennsylvania Hospital and divided into three groups similar as to age, and degree of circulatory efficiency. The clinical course of the three groups was followed for nine months on the three respective preparations of digitalis. During the subsequent six months four of the nine members of the group which had previously received the preparation containing only the glucosides were changed to the commercial whole leaf tablet and the others were given the American Heart Association product. Five of the seven patients originally given the commercial whole leaf product were changed to the glucoside preparation and the remainder were given the A H A product, six members of the group started on the A H A product were then placed on the glucoside tablet and three were given the commercial whole leaf product. Each patient reported to the cardiac clinic at intervals of from one to four weeks for a check up of symptoms and a physical examination, which included a vital capacity determination. Orthodiagnostic and electrocardiographic studies were made every three or four months. During our study of more than 18 months no striking difference was observed in the general clinical picture including the ability to work of the members of the three groups.¹³

The final check up of the original 25 patients with whom the study was begun in 1931 is of interest. Twelve patients are still living and

11 of these are still regular attendants at the cardiac clinic. Of ten patients with marked cardiac enlargement only three are living. Six of 11 patients with moderate cardiac enlargement are alive and of four with slight enlargement three are in relatively good health and working.

Our second study was with verodigen—a gitalin glucoside of digitalis. Five patients with established auricular fibrillation and one patient with auricular flutter, all previously untreated with digitalis were digitalized with this drug as were two patients with regular sinus rhythm and

TABLE II

CLINICAL COURSE OF W. S., A WHITE MAN AGED 38 WHO HAD RHEUMATIC HEART DISEASE WITH MITRAL STENOSIS AND AURICULAR FIBRILLATION

Date	6/9*	6/23	7/11†	8/1	8/29	9/12
Average daily dose grains	1/1200	1/1200	1/600	1/300	1/300	1/300
Weight pounds	128	131	129	130	132	135
Ventricular rate	84	100	120	84	80	60
Pulse rate	84	100	112	84	80	60
Dyspnea	0	0	0	0	0	0
Edema	0	0	0	0	0	0
Lungs (râles)	0	0	0	0	0	0
Liver cm palp	0	0	0	0	0	0
Blood pressure	120/0	120/70	130/70	110/70	120/60	110/70
Vital capacity cc	3100	3000	3300	3200	3200	3100
Complaints	None	None	None	None	Ano- rexia	Ano- rexia

* Condition controlled on $\frac{1}{600}$ grain of digitaline (Nat. velle) for eight months prior to this date. A daily dose of $\frac{1}{1200}$ grain started on this date.

† Daily dose of $\frac{1}{600}$ grain resumed on this date.

advanced congestive heart failure. Of the ambulatory patients whose established auricular fibrillation had previously been controlled with whole leaf digitalis preparations or digalen, 14 were given verodigen. Clinically we found 0.26 mg ($\frac{1}{40}$ grain) of verodigen to be equivalent to one cat unit (approximately 0.1 Gm—11½ grains of powdered digitalis) and the total dose necessary for digitalization from 3 to 5 mg ($\frac{1}{20}$ to $\frac{1}{12}$ grain) administered over five or six days. The most frequent adequate maintenance dose of verodigen was 0.26 mg ($\frac{1}{40}$ grain) daily.¹³

For about one year our study was concerned with digitaline (Nat. velle). Twelve patients with heart disease who had previously received

no preparation of digitalis were digitalized by this glucoside. Eighteen patients whose established auricular fibrillation had previously been controlled by one or more preparations of digitalis were given digitaline. The average period of observation for this group was $10\frac{1}{2}$ months. The total dose necessary for digitalization varied from 1 g to 2 mg ($1\frac{1}{10}$ to $1\frac{1}{10}$ grain) when administered over five or six days. The most frequent adequate maintenance dose was 0.11 mg ($\frac{1}{600}$ grain) daily.

A further study was made with digoxin*. It was carried out in a similar manner and 27 patients were observed. Six of them had never previously received digitalis in any form and the remaining 21 had been maintained with one or more other preparations of digitalis. The average period of observation of the latter group was $8\frac{1}{2}$ months. The most frequent satisfactory maintenance dose of this product was approximately 0.1 mg ($\frac{1}{160}$ grain) daily, and we feel that this dose is clinically the equivalent of one cat unit of standardized digitalis leaves.

The following case presents an example of the type of ambulatory patient observed. The data recorded are a portion of those obtained during a $1\frac{1}{2}$ year period of observation while the patient was receiving five different preparations of digitalis. The effect of stopping all medication for a few weeks is well shown. The gradually decreasing vital capacity is of interest. Clinically there was no change in the patient's condition during the study.

S. F. a Jew, aged 32, complained of rapid heart action of three months' duration, with fatigue, dyspnea on exertion and cough. On his first visit to the Cardiac Clinic of the Pennsylvania Hospital in June, 1931. At the age of 15 years he had been told that he had a heart murmur; however, he had been in excellent health and had been very active physically previous to 1931. Physical examination revealed cardiac enlargement, mitral stenosis and insufficiency and auricular fibrillation without any signs of congestive failure. Since 1931 he had been taking digitalis regularly.

The cardiovascular diagnosis was as follows: *A* Unknown (toxicosis); *B* cardiac enlargement, mitral stenosis and insufficiency; *C* auricular fibrillation; *D* Class 2a. The clinical course is shown in Table I.

* The manufacturers of verodigen—Merck & Co.—and of digitaline (Nativelle)—F. Fougere & Co., Inc.—claim that their preparations are pure stable crystallized glucosides isolated from the leaves of digitalis purpurea and the main factors of digoxin—B. Brown & Weller & Co.—claim that it is the same type of glucoside isolated from the leaves of digitalis lanata. If these claims are true, these three preparations should keep identically and the dose can be determined by weight with out the necessity of an animal bioassay.

The data in Table II show the effect of increasing or decreasing the maintenance dose of a digitalis preparation in treating a condition previously well controlled on the same preparation

Our most recent study was made with uarginin. Other interesting observations upon the use of this drug will be found in papers by Chamberlain and Levy,¹⁴ Carr and Mayer,¹⁵ and Maher and Sittler.¹⁶

Because of the somewhat variable clinical results obtained by other investigators, especially in relation to the toxic effects and the duly maintenance dosage, and in view of the increasing use of the glucoside preparations of squill in all types of cardiac disease, further clinical studies with this drug are desirable.*

Use of the drug for a period of several months in the same patient and a comparison of its action with that of digitalis in various types of heart disease seemed especially indicated

METHOD

In this study, we have followed the plan used previously in evaluating various preparations of digitalis.¹¹⁻¹⁷

There were essentially two groups of cases: (1) Patients with severe heart disease and cardiac decompensation who had previously received no preparation of digitalis. These cases were hospitalized and, whenever possible, were given two or three days' bed rest to serve as a control period before any cardiac drug was given. (2) Patients with chronic auricular fibrillation who had been previously controlled on one or more preparations of digitalis over a period of one or more years. These were ambulatory cases of rheumatic or arteriosclerotic etiology, most of whom had been followed for several years. During this time, the maintenance dose of the various digitalis preparations had been determined by careful clinical observation. That digitalis was essential to the well being of these patients was proved to our satisfaction by cessation of the drug (voluntary or directed), and the development of symptoms and signs of myocardial insufficiency after a variable period, usually from three to six weeks.

A summary of 16 patients with congestive heart failure who had previously received no treatment with digitalis preparations reveals that

* We are indebted to the Calco Chemical Company Inc. for the large amount of uarginin used in this study. This drug is fully described in New and Non-Official Remedies. The water-insoluble glucosides of squill (*Urginea maritima*) contained therein are standardized chemically, physically and biologically.

ten were of the rheumatic type four arteriosclerotic and two arteriosclerotic and hypertensive Persistent auricular fibrillation was present in 11 of the 16 patients The lowest number of tablets of 0.5 mg ($\frac{1}{420}$ grain) necessary in a four to six day period for a satisfactory therapeutic effect was 25 the greatest number 59 with an average of 36.3 There are approximately 90 cat units in 36.3 tablets of arginin which is equivalent to 18 cat units or 27 grains of digitalis

These patients were acutely ill and were treated individually rather than by a standard routine As mentioned whenever possible a control period of two or three days was allowed before any specific cardiac drug was given The usual laboratory procedures were done including frequent electrocardiograms An initial dose of six to eight tablets of arginin (0.5 mg— $\frac{1}{420}$ grain—each) was given orally followed by two tablets three or four times daily By this method the patients were usually digitalized in three to six days Anthion or mercurial diuretics were used whenever indicated but were withheld until after sufficient time had elapsed to allow diuresis from arginin whenever the condition of the patient warranted Following improvement the maintenance dose of arginin was determined for each patient by clinical trial and they were continued on this drug over a period of several months in most instances

The following case report is an example of the patients in the first group

Case R. G. (No. 15645) white male aged 31 was admitted to the Pennsylvania Hospital on July 22, 1937 complaining of shortness of breath cough and abdominal distress *H P I* The patient stated that he had been in good health prior to the present illness and had been able to do ordinary labor without difficulty though he did admit to shortness of breath on moderate exertion for several years For two weeks prior to admission he had noted palpitation shortness of breath and weakness He could not sleep lying down and epigastric distress and nausea were present He had vomited several times during this period Dyspnea was quite marked after July 18 so that he was orthopneic and cough was a distressing factor He had received no medical care prior to hospitalization *I H* The patient's father died at 33 years of age from pulmonary tuberculosis *S H* In the shoe business until 1935 Worked for W. A. two years stopping on June 15, 1937 as the job was finished Moderate user of alcohol and tobacco *P M H* Chicken pox and pertussis as a child Frequent rheumatism until 15 years of age This was often so

severe he could not walk but he was not confined to bed with it at any time. He denied scarlet fever, chorea, diphtheria, respiratory trouble or cardiac disease. Chancre in 1928 with 14 injections of an arsenical preparation. No operations.

Physical examination revealed a large slightly obese man sitting up in bed with definite dyspnea. No cyanosis or jaundice were present. The eyes, ears and nose were negative. The teeth and tonsils were definitely diseased. The chest was symmetrical and moved equally. The lungs were clear anteriorly but posteriorly there were subcrepitant rales at the left base and dullness below the level of the seventh rib on the right with diminished breath sounds and *fremitus*. The apex beat of the heart was felt 13 cm. to the left of the midsternal line in the sixth interspace. The right border of cardiac dullness was 5 cm. from the midline in the fourth right interspace. A soft systolic murmur was heard at the apex and there was a questionable short rumbling diastolic murmur at this area. The pulmonic second sound was accentuated, ventricular rate 152. Rhythm totally irregular. Pulse rate 110. The abdomen was obese with a sense of resistance in the right upper quadrant but no organs were palpated. Slight edema of the ankles was present and the tendon reflexes were hyperactive.

Laboratory Findings Urine eight specimens essentially normal. Blood count: Hemoglobin 83 per cent, RBC 5,560,000, WBC 12,200. Differential and smear normal. Blood Wassermann strongly positive. Cerebrospinal fluid Wassermann negative. Blood sugar 98 mg. per cent. Blood urea nitrogen 11.2 mg. X-rays of chest: Considerable cardiac enlargement in the regions of both the right and the left ventricles and the left auricular appendage. The lung fields were clear except for an old organized tuberculous lesion in the left midlung field.

Clinical Course The patient was started at once on uginin and was given an initial dose of six tablets (0.5 mg. each) followed by two tablets three times daily for the next six days. The patient was at rest in bed with no medication except 0.01 Gm. ($\frac{1}{100}$ grain) of morphin on the first night. The fluid intake was limited to 1500 cc. (48 ounces) daily. The patient improved rapidly and by the sixth hospital day the ventricular rate was 80 with no pulse deficit. Thirty-eight tablets of uginin had been given during this period. (From our later conclusions this would be the clinical equivalent of about 19 cat units or 1.814 Gm. (28 $\frac{1}{2}$ grains) of standardized digitalis leaves.) The dosage of the drug was then gradually diminished and he was placed on a maintenance dosage of two tablets daily on August 1, 1937. The patient was gradually allowed up starting August 18, 1937. It seemed wise to increase the maintenance

dose to 3 tablets daily on this date, and this was continued until his discharge September 1, 1937.

Final Diagnosis

1. Heart disease

(a) Rheumatic type.

(b) Cardiac enlargement, mitral stenosis and insufficiency

(c) Auricular fibrillation

(d) Class 2A.

2 Syphilis—latent

TABLE III
LATER CLINICAL COURSE OF PATIENT R. G

Date	10/7	10/21	12/9	2/3	4/7	7/28
Drug	Urgimin	Same	Same	Digitalis	Same	Same
Daily dose	Tab 3*	3	3	gr 1½†	1½	1½
Weight	212	214	213	210	212	207
Ventricular rate	98	64	66	68	76	60
Pulse rate	78	64	66	68	76	60
Dyspnea	0	0	0	0	0	0
Edema	0	0	0	0	0	0
Lung (râles)	0	0	0	0	0	0
Liver, cm palp	0	0	0	0	0	0
Blood pressure	110/70	110/70	120/70		120/70	136/80
Vital capacity, cc	3500	3800	2500	3700	3700	

* Tablets of urgimin, 0.5 mg each. This dose had been given daily for seven weeks prior to this date. The dose was increased on this day to three more tablets per week (24 per week).

† Tablets of standardized whole leaf digitalis, 0.1 Gm (1½ grains), equal one cat unit. The patient was changed to this medication on this date, having received three tablets of urgimin daily since October 21, 1937.

The second group consisted of patients with organic heart disease who had previously been maintained in a satisfactory condition by the use of one or more preparations of digitalis.

The following table is a summary of 18 patients with chronic auricular fibrillation who had been previously controlled on various digitalis preparations for periods of 18 months to 6 years (ten cases followed for over five years) followed by urgimin therapy for 5 to 14 months (average of 11.5 months each).

TABLE IV
DAILY MAINTENANCE DOSE

1 case	3 tablets
9 cases	2 tablets
1 case	2 tablets
7 cases	1 tablet
Average of all cases equals 1.7 tablets	

RESULTS

11 cases	No change in condition
2 cases	Not as well?
2 cases	Congestive failure Better with digitalis
1 case	Congestive failure Better in hospital
1 case	Ventricular rate poorly controlled
1 case	Died No relation to therapy?

TABLE V

CLINICAL COURSE OF W. S. (No. 1854), A WHITE MALE, AGED 41, WITH RHEUMATIC HEART DISEASE MITRAL STENOSIS AND AURICULAR FIBRILLATION DATA TO SHOW THE RESULTS OF INCREASING AND DECREASING THE DAILY DOSE OF URGININ

Date	10/8/37	12/2/37	12/23/37	2/24/38	3/1~/38	3/31/38	4/14/38	5/20/38
Medicine	Urginin	0	Urginin	Urginin	Urginin	Urginin	0	Digitalis
Daily dose	Tab 1*	0	Tab 2	Tab 2	Tab 3	Tab 4	0	started
Weight (lbs.)	128	132	131	134	137	136	137	139
Ventricular rate	76	80	122	74	72	68	44	108
Pulse rate	76	80	108	74	72	68	44	92
Dyspnea	0	0	0	0	0	0	0	0
Edema	0	0	0	0	0	0	0	0
Lung (râles)	0	0	0	0	0	0	0	bases
Liver, cm palp	0	0	0	0	0	0	0	0
Blood pressure	130/80		120/70		150/100	110/80	140/90	130/80
Vital capacity, cc	3300	3000	2900	2900	3000	3000	2900	2700

* The patient had been controlled on one tablet of urginin (0.5 mg.) daily for seven months prior to this date. The daily dose listed in any column is carried over to the next date. The patient was seen at two to four weeks intervals so only a part of our observations are listed above.

Table V shows the effect of increasing and decreasing the daily dose of urginin in a patient with rheumatic heart disease and auricular fibrillation. The patient had been on a maintenance dose of one tablet of this drug for several months. (This was probably about the minimum

maintenance dose rather than the optimum) After stopping the drug for three weeks the ventricular rate had risen to a fairly high rate with a moderate pulse deficit On resuming the medication the ventricular rate returned to a normal level and remained there despite a considerable increase in the daily dosage After four weeks on a maintenance dose of uginin probably well above the ideal dose the ventricular rate fell to a low level but there were no other signs or symptoms of overdosage All medication was again stopped and even after a period of six weeks the ventricular rate had not risen to the high level previously attained after only three weeks of no medication These findings compare favorably with similar studies on this patient with several digitalis preparations and emphasizes the fact that the difference between the *minimum effective dose* and the *maximum dose tolerated* without toxic effects may be considerable They also suggest that the rapidity of excretion of the drug is probably quite similar to that of digitalis and that this factor is influenced considerably by the amount of the drug previously taken

The results in the 18 patients with auricular fibrillation who had previously been well controlled on digitalis preparations and were then placed on uginin therapy can be summarized briefly as follows Eleven patients were equally well controlled on uginin therapy in two patients the ventricular rate was well controlled but the patients did not seem as well as on digitalis therapy though frank cardiac failure did not occur the difficulty in controlling the ventricular rate was encountered in one case after apparently sufficient dosage two patients who developed congestive heart failure on uginin therapy despite increasing the drug to the point of toxicity were improved by the maintenance dose of digitalis which had previously been effective one patient developed congestive heart failure probably because of progressive cardiac damage but seemed somewhat better on subsequent digitalis therapy one patient died during the study with probably no relation to the therapy employed

The daily maintenance dose of uginin is determined by clinical trial in these 18 patients with chronic auricular fibrillation and in the entire group of 40 patients is shown in Table VI It is seen that the most frequent maintenance dose of the drug is 1 to 2 tablets (1 mg) daily and that the average maintenance dose of the whole group is approximately this same figure

TABLE VI

DAILY MAINTENANCE DOSE OF URGININ IN 18 PATIENTS WITH CHRONIC AURICULAR FIBRILLATION WHO HAD BEEN CONTROLLED PREVIOUSLY ON VARIOUS DIGITALIS PREPARATIONS

<i>Number of Cases</i>	<i>Tablets</i>
2	3
10	2
6	1

Average daily maintenance dose of the 18 cases, approximately 18 tablets each

DAILY MAINTENANCE DOSE OF URGININ IN ALL OF THE 42 PATIENTS TREATED IN THIS SERIES

<i>Number of Cases</i>	<i>Per Cent</i>	<i>Tablets</i>
3	7.1	4
5	12.0	3
27	64.3	2
7	16.6	1

Average daily maintenance dose of all 42 cases, 2.1 tablets or 1.05 mg each

TABLE VII

COMPARISON OF DIGITALIS PREPARATIONS USED CLINICALLY AT THE PENNSYLVANIA HOSPITAL FOR AN EIGHT YEAR PERIOD

The clinical equivalent of approximately *one cat unit* is shown in grains after each preparation. This is the average daily maintenance dose. The second column is the average full digitalization dosage given over a period of three to six days.

<i>Name of Preparation</i>	<i>Grains</i>	<i>Grains</i>
American Heart Association		
Whole Leaf Tablet	1½	18 to 30
Burroughs Wellcome & Co		
Whole Leaf Tablet	1½	18 to 30
Digalen	1½	18 to 30
Verodigen	½ ₂₄₀	½ ₂₀ to ½ ₁₂
Digitoline—Nativelle	⅙ ₃₀	⅙ ₀ to ⅙ ₃₀
Digoxin	⅙ ₆₀	⅙ ₁₃ to ⅙ ₈
Urginin	⅙ ₆₀ *	⅙ ₅ to ⅙ ₃

* Two tablets

COMMENT

In estimating the results obtained in a clinical study of this type many factors other than the medication employed are concerned with the well being of the patient. With any drug prolonged in action, observation of the patient over a period of months is essential. The natural history of the cardiac disease must be considered, as the pathological lesion tends to be progressive in many of these cases. In a given patient, using digitalis or a drug of similar action, there is usually a considerable difference between the minimum effective dose and the maximum tolerated dose. The optimum maintenance dose of a drug of this type is somewhere between these two extremes, and it can be determined accurately only by clinical observation. In patients with severe myocardial damage, the margin of safety between effective and toxic doses is often narrow. In some instances toxic effects appear before beneficial effects are manifest. Obviously, in these latter cases little or no benefit is derived from the use of the drug, and the course usually is unfavorable.

Previous experience with glucoside preparations of digitalis taught us to be cautious in judging the probable oral dose in man from the cat unit standard of the same preparation. This truth was again evident in this study, when it was found that the drug used (urginin) was several times less potent than digitalis leaves in the same cat unit dosage if both drugs were given orally. This fact of course, does not interfere with the determination of the proper dosage by clinical trial, or with the efficacy of the drug if a sufficient amount of it is given. It does suggest that the drug is insufficiently absorbed or partially destroyed by the gastrointestinal tract, or more rapidly excreted as compared with digitalis. More than one of these, or even other factors may be operative in this regard.

Our observations on urginin confirm those of previous authors who stated its action was similar to that of digitalis. In patients with cardiac failure, whether or not auricular fibrillation was present, beneficial effects followed its administration in nearly all cases. The ability to slow the ventricular rate in patients with auricular fibrillation was fully as striking as that of digitalis. The effect on the rate with normal sinus rhythm was much more difficult to evaluate and certainly was not very significant. *There was no evidence of a direct diuretic effect of the drug, the diuresis in edematous patients following improvement in the circulation, as occurs with digitalis.* The effect on the electrocardiogram was similar to

that of digitalis with a delay in the A V conduction time in some patients and a depression of the R S T segments when full doses were given. The rapidity of action when given orally was comparable to digitalis in the equivalent dosage. On cessation of the drug after a maintenance dose had been given for some time its effect still was evident for a period of two to five weeks, the variation in time probably depending on both individual differences and whether the daily dose was near the maximum or minimum for that patient. This compared favorably with the results in the same patients in previous studies with digitalis preparations.

Toxic effects of uarginin were also similar to those of digitalis. Perhaps the most difficult toxic manifestation to evaluate in digitalis preparations or drugs of this type is that of nausea and vomiting. The other authors cited who have worked with uarginin felt nausea and vomiting was less frequent in therapy with this drug than with digitalis preparations. In our cases two patients developed nausea and vomiting after a large initial dose of the drug (six to eight tablets) but were able to take the drug in divided doses. This was not considered a manifestation of toxicity. Two patients on a maintenance dose of the drug developed these symptoms as a definite evidence of toxic effect. Diarrhea developed in two patients who were on a maintenance dose of uarginin and the symptoms seemed definitely related to the drug. They were able to take digitalis without similar difficulty. Disturbances in rhythm occurred in several patients receiving uarginin therapy. One patient who had been getting full maintenance doses of the drug (three tablets daily) developed ventricular tachycardia within a few hours after receiving 0.5 Gm ($7\frac{1}{2}$ grains) of digitalis given in error. Two patients developed coupling of *ventricular premature beats and one patient auricular fibrillation* as a manifestation of toxic effect. In all three the abnormal rhythm stopped on cessation of the drug. One patient with rheumatic heart disease and bronchopneumonia developed auricular fibrillation during the course of the infection. On uarginin therapy he improved somewhat and reversion to normal rhythm occurred but the patient succumbed a few days later. One patient with congestive heart failure had auricular fibrillation and frequent premature beats on admission. Some clinical improvement occurred and the rhythm reverted to normal but the premature beats continued. Later an A V nodal rhythm was present and the clinical

course was not satisfactory although the patient survived. In one case with normal rhythm and frequent premature ventricular contractions the arrhythmia persisted after urginin therapy though there was clinical improvement.

It is very probable that the incidence of toxic effects in the use of any drug of the digitalis type depends largely on the severity of the cardiac damage in the patients, the care with which the drug is given and the point to which the physician is willing to go in the attempt to get beneficial effects. With slightly damaged hearts nausea and vomiting are apt to appear before disturbances in rhythm but with severe disease of the myocardium disturbances in rhythm and conduction may occur with relatively small amounts of the drug and often with no tendency to gastrointestinal symptoms which suggest toxicity.

True idiosyncrasy to digitalis probably is rare but gastrointestinal disturbances and other subjective symptoms are not uncommon with digitalis therapy. It is in these cases that a drug of the type of urginin is especially indicated.

Finally we believe the results of a clinical study of this type must be interpreted in the light of the normal variations and the personal element involved. It is essential that a large number of patients be observed over a considerable period of time. (One of us has personally observed all the patients included in this study.) The natural history of disease must be considered and gradual progression of the pathological lesion is to be expected in many cases. Complications especially infectious or embolic may alter the course of the disease. It is wise to include patients who have never previously received any preparation of digitalis. Patients with established auricular fibrillation and inherently rapid ventricular rates are the most satisfactory when one is judging the digitalizing and the maintenance dose of a given preparation.

There seems to be little relation between the weight of the patient and these doses. For practical purposes the weight need not be considered. The important point is to give the patient a sufficient amount of the preparation avoiding overdoses. In a given patient this amount can be determined only by clinical trial. *It should be remembered that the more severe the heart damage the less the margin of safety in using digitalis preparations.* With a bad myocardium toxic rhythms (prema

ture beats, coupled rhythm and ventricular tachycardia) may appear before nausea and vomiting or other signs of an overdose.

The release of digitalis preparations or other similarly acting drugs before the dosage and efficacy are determined by adequate clinical trial is to be deprecated. The dosage determined by biologic assay may have more or less than the predicted potency when the drug is administered orally to man. Experience with one product in which the strength for man was three times that predicted by the biologic assay¹¹ has led us to be cautious in evaluating these products on the basis of animal experimentation.

A better result from a given product of digitalis may be due to a relatively greater amount of potent substance rather than to a greater efficacy of the product as compared to some other preparation. This fact probably accounts for much of the improvement seen in patients after they change from one preparation to another.

It has long been known that potent preparations of digitalis produce nausea and vomiting if given in sufficient doses. We have observed these symptoms with all glucoside preparations studied. Other manifestations of toxicity, such as coupling of premature beats, were also noted in all instances. There was no evidence that digitalization was effected more rapidly with any of the glucoside preparations than with digitalis leaves, when given by mouth. *After cessation of the drug in a fully digitalized patient, "digitalis effects" seemed to persist for about the same length of time (from three to six weeks) with the various preparations.*

All the glucoside preparations tested were uniformly potent and stable. The clinical results were similar and equal to those of standardized digitalis leaves when given in sufficient doses, but they were in no way superior. If these preparations are pure substances, as claimed, it would seem safe to dispense with biologic assay, which would reduce the cost of manufacture considerably.

It is possible that in the future the chemical isolation and standardization of digitalis glucosides may be the method of choice in producing preparations for clinical use. It seems logical, however, if all the glucosides are potent when given orally to man, that the whole leaf which contains all these substances may be preferable clinically.

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CHAPTER XXXII

THE PREVENTION AND RELIEF OF HEART DISEASE AS A PUBLIC HEALTH PROBLEM

By H M MARVIN M D

Not infrequently during the past few years the statement has been made that heart disease as a public health problem is receiving insufficient attention. This is not surprising in view of the wide publicity accorded the statistics indicating a steady increase in the mortality from diseases of the heart which have aroused grave concern among those who have not troubled to analyze them and consider their implications. Actually the available evidence would seem to indicate that the rising mortality rates ascribed to diseases of the heart may be interpreted as a tribute to the increasing efficiency of public health measures rather than as an indictment of them.

One reason for the concern that has found expression in criticism undoubtedly lies in the failure of most laymen (and many of those who write and speak on this subject) to discriminate between different types of heart disease. They think and speak of heart disease as a single entity which it is not; they view with alarm the appalling increase in the death rate from heart disease although the increase is largely confined to a single type of heart disease and probably does not justify the alarm that has been expressed. From the standpoint of numerical incidence the important types of heart disease in the United States are four in number; they are caused respectively by rheumatic fever, syphilis, hypertension and arteriosclerosis of the coronary arteries. These four types probably constitute from 90 to 95 per cent of all heart disease in this country today and the small amount due to other causes may be ignored for our present purposes; subsequent statements should be understood as applying only to these four groups.

Etiology. In considering the etiology of the four conditions just named it should be noted that one (syphilis) is due to infection by a

known agent one (rheumatic fever) is possibly infectious in nature and the remaining two are thought to have no relation to infectious processes. With the single exception of syphilis the causes are unknown. Now there is general agreement that the great increase in the death rates ascribed to diseases of the heart in recent years has been due almost entirely to a rise in the mortality from the arteriosclerotic type. Thus it need hardly be stated occurs among the older groups of the population. As the diseases of infancy, childhood and early adult life have been conquered or lessened by preventive measures or more intelligent treatment it is clear that a larger number of people will live to old age and must die of conditions that occur in later life, in other words of the so-called degenerative diseases. Arteriosclerosis appears to be the one process that is most nearly universal in elderly people and it is inevitable that the vessels of the heart, brain and kidneys should be involved in a high percentage.

For reasons that are only partly known the heart is affected to a serious degree more often than the other vital structures and degenerative processes in this organ become the immediate cause of death. Far from being a cause for adverse criticism of medical practice and public health efficiency this fact should be a cause for congratulation since it is a reflection of and an inevitable result of the increasing average age of the population. Broadly speaking the aim of preventive medicine should be to enable every individual to avoid or survive the diseases of early and middle life and to succumb ultimately to one of the diseases associated with old age. Of these arteriosclerosis of the coronary arteries happens to be the most frequent at the present time.

The general truth of the foregoing statement is now fairly widely recognized and accepted but *this acceptance has not led to a perceptible diminution in the frequency of the statements that the public health aspects of heart disease are being neglected.* A very brief consideration may possibly indicate that these statements are not wholly justified.

The diseases usually regarded as falling within the jurisdiction of public health officials or a proper subject for study by them have certain features in common. They may threaten the health of large groups of people because they are related to contamination of foods (milk, sea foods, meats) or the water used for drinking. They may affect the public health because of the possibility of direct or indirect spread of the disease to

Pioneers in the Advance of Cardiology by Methods of Clinical Observation



Auenbrugger, in 1761, added percussion to the Hippocratic method of inspection as a means of diagnosis of disease. His results were recorded in a brief, modest text, 'On Percussion of the Chest,' one of the great classics of medicine.



Corvisart revised and taught Auenbrugger's new method of percussion and secured for it a wide adoption. His treatise on heart disease published in 1806 advanced the study of cardiac symptomatology and contains the first description of the presystolic thrill of mitral stenosis.



Laennec, after mastering percussion under the guidance of his teacher, Corvisart, invented the stethoscope in 1816 giving to physicians of his day trained in inspection and percussion, the method of auscultation. This new aid to diagnosis and its application to diseases of the heart and lungs was fully described by Laennec in 1819 in his famous 'Traité de l'auscultation médiate.'



Hope aided in popularizing Laennec's discovery and advanced the study of Clinical Cardiology in 1831 by the publication of a book on, 'Diseases of the Heart and Great Vessels.' He clearly described the clinical features of mitral regurgitation, aortic stenosis and aneurysms.



William Stokes, a master in the art of clinical observation and using in addition the newer methods of percussion and auscultation, gave clearcut descriptions (1837) of diseases of the heart and the two well known syndromes—Stokes-Adams disease and Cheyne Stokes respiration. He is also credited with the first account of paroxysmal tachycardia.

others, as in the case of diphtheria, scarlet fever, smallpox, and other acute contagious diseases. They may become a matter of public concern because they have a high incidence and high mortality rate, yet are subject to effective curative treatment; acute lobar pneumonia might be cited as an example of this type. But it is to be noted that in almost every instance the diseases now under discussion have specific and known causes, their methods of spread are understood, and they are often subject to prevention by means of proper measures.

These statements cannot be applied to diseases of the heart, with the single exception of the syphilitic type. This is the one type of which the cause is known; it is the one that may be abolished by prevention, or by early and adequate treatment of the syphilis which is the specific cause. In so far as the present public health campaign against syphilis proves successful in reducing the incidence of the disease, just so far will the deaths from syphilitic heart disease decrease. But numerically this is the least important of the four major types of heart disease. The other three probably comprise 90 per cent of the cases included in this discussion. The causes of these three are unknown. There is no known method of preventing their occurrence and development. There is no form of treatment that will satisfactorily retard their rate of progress or protect the heart from their effects. The patient who suffers from any of them is not a menace to his fellows, he has not developed his disease (so far as is now known) through any remediable failure of medical or community efforts, and his illness is not subject to specific curative treatment. His heart disease is an individual, personal problem, of interest to the public and to health officers only because of the high mortality rates charged against it.

For these and other reasons, diseases of the heart are not usually regarded by authoritative observers as constituting an important public health problem. A survey of current textbooks and monographs devoted to public health and preventive medicine discloses that they either do not mention heart disease at all, or dismiss the subject with a few words

PREVENTION

From the standpoint of prevention, there is but little that can be said with confidence. In the absence of any specific factors that can be regarded as a cause of arteriosclerosis, this is now generally regarded as a process of ageing of the artery. The oft expressed hope of preventing

arteriosclerosis is actually a hope of preventing the body from growing old as years pass and there is as yet little basis for it. Similarly the cause or causes of hypertension remain obscure although the experimental work of Goldblatt may ultimately prove to have indicated that its etiology lies in alterations of the renal function not discoverable in their earlier stages by the methods now available. Until the cause is known and a method found for abolishing or curing the etiologic condition one cannot hope to prevent hypertension or hypertensive heart disease. At present there is no curative method known for either the hypertension or the enlargement of the heart and heart failure that result from it.

Rheumatic heart disease occupies a slightly different position. Arteriosclerotic heart disease as already emphasized affects mainly the older groups of the population and is often but one of several important degenerative processes that are progressing simultaneously. Even if it were possible to cure the sclerotic process in the heart it is clear in many instances that the patient would succumb to other chronic changes in the prostate the kidneys the lungs nervous system or gastrointestinal tract. Expressed otherwise the cure of arteriosclerotic heart disease would not restore the individual to a normal healthy state except in a small and unknown percentage of cases. But rheumatic heart disease occurs predominantly among children and young adults and causes widespread crippling and death in the earlier decades of life. The lesion in the heart is often the only abnormality from which they suffer. If rheumatic fever could be prevented or cured before it results in cardiac injury thousands of patients would be enabled to have normal healthy activity during the productive years of early and middle adult life. The prevention of rheumatic diseases becomes therefore a matter of the most urgent concern and one that may properly engage the attention of government and public health officers. In the past few years attention has been sharply focussed upon poliomyelitis as a cause of crippling in childhood. Heartfelt sympathy has been widely expressed and millions of dollars have been contributed for the study and relief of the disease. But it is relevant to point out that from the standpoint of its incidence its permanent effects upon those who survive and its mortality rate infantile paralysis is almost infinitely unimportant in comparison with rheumatic heart disease. The problems relating to the rheumatic diseases are far more urgent and their magnitude far greater than those

created by poliomyelitis, and there can be no question of the wisdom of devoting more time, thought, and money to their solution.

For the above reasons, among others, diseases of the heart have not been subject to the preventive measures generally applied to acute infections and to such diseases as pulmonary tuberculosis. Unfortunately, diseases of the heart (except that due to syphilis) are not preventable. Attention has therefore been focussed largely upon the attempt to retard the progress of cardiac lesions, and thus postpone the onset of heart failure, by enforcing the best possible treatment after the presence of heart disease has been discovered.

It has been suggested often that rheumatic heart disease should be treated along the same general lines as pulmonary tuberculosis, by means of long periods of bed rest in sanatoria. This suggestion, which is superficially attractive (and in many cases valuable) overlooks two important considerations. The tuberculous patient is a menace to others; the cardiac patient is not. The patient who has pulmonary tuberculosis, unless the process is far advanced, may have reasonable assurance that proper treatment will result in arrest of the disease for an indefinite period and only slight modification of his normal life and activities. No such assurance can be given truthfully to the patient who has rheumatic heart disease. However long the initial period of rest and however careful the subsequent life, reactivation of the lesion in the heart or its steady progress to congestive heart failure occurs in a distressingly high proportion of cases. Expressed otherwise, the prognosis for life and activity is excellent in most cases of pulmonary tuberculosis if the disease is discovered early and treated properly, while it is poor in most cases of rheumatic heart disease.

The foregoing remarks may seem to emphasize unduly the discouraging aspects of heart disease and our deplorable lack of knowledge as to the cause, prevention, and cure of the most important types. They are not intended in any spirit of pessimism or hopelessness, they are merely a brief and inadequate statement of some of the reasons why diseases of the heart have not been, and cannot well be, explained to the general public as certain other diseases have been. In the case of cancer and tuberculosis, for example, the public may be truthfully assured that early recognition and prompt treatment will often result in virtual or complete cure and in indefinite extension of an active, healthy life. No such statement can

be made with respect to diseases of the heart. The general public is already far too conscious of its heart and of the various serious things that may happen to it, if the full truth (as distinguished from the encouraging brilliant exceptions) were made known, it would in all probability cause a great increase in anxiety and apprehension.

The hope for amelioration of the present situation, therefore, lies in better treatment of the individual patient until such time as preventive or curative measures may be discovered for rheumatic fever, hypertension, and arteriosclerosis. This, in turn, means greater emphasis upon education of the physician and less upon education of the layman. It means that every contribution to prevention, diagnosis, or treatment should be made known without delay to the practicing physicians throughout the country. It involves unremitting attempts to raise the standards of treatment in private homes, cardiac clinics, hospitals, and convalescent homes. And it means, more than all else, unceasing efforts to find the cause or causes of the etiologic diseases, since all hope of prevention or cure rests ultimately upon this knowledge.

There is but one national organization in the United States which is devoted to an attempt to apply the general principles set forth above. It is the American Heart Association, and the chief purpose of the present chapter is to review briefly its origin, work, and aims for those readers who may be interested.

THE ORIGIN AND WORK OF THE AMERICAN HEART ASSOCIATION

HISTORICAL*

It is perhaps impossible to state definitely where and when the ideas were born that led ultimately to the formation of the American Heart Association; indeed, it is highly probable that similar thoughts came to many physicians in different parts of the country at about the same time. But the acts which appear in retrospect to have been most influential occurred in the year 1912, and were two in number. In that year Dr. Hubert V. Gimle and his social service assistants at Bellevue Hospital in New York City began a careful and tedious study of cardiac patients

* For this account of the formation of the American Heart Association and of the events preceding and immediately following it the writer is indebted to the generous help of Dr. Robert H. Halsey, who played such an important part in its development. Dr. Halsey has written a full account of the history of the Association and the present notes are taken from it with his permission.

which continued for three years the results were published in 1914 by Miss Katherine Tyng in her Report of the Social Service Bureau of Bellevue and Allied Hospitals. This study demonstrated conclusively that many adult patients who had heart disease could continue at self supporting occupations if their work was carefully selected and the patients themselves properly supervised. Careful attention to the home environment and conditions of work, as well as frequent examinations of the patient resulted in a decrease in the episodes of congestive heart failure. Twenty eight years later this truth seems to be self evident but apparently this three year study was the first conclusive group demonstration of the great value of careful constant supervision of the cardiac patient in the clinic, in his home and in his occupation.

In the same year, the same general ideas were given practical application by the organization under the wise and skillful guidance of Dr Lewis A. Conner, of the Trade School for Cardiac Convalescents or Sharon Shop which had its workshops in Sharon Conn. and its office in New York City. This trade school was frankly experimental and the patients were very carefully selected but after a sufficient period of observation it seemed to be clearly demonstrated that many cardiac patients could perform suitable work not only without injury to themselves but also with actual improvement in their general health.

As evidence of similar interest in other cities in the problems of heart disease it should be mentioned that in 1910 Dr Fritz B. Talbot and Dr Richard M. Smith of Boston had established a Children's Heart Clinic for the purpose of studying acute endocarditis in childhood. The conduct of this clinic was later assumed by Drs. Richard Lustis and Paul D. White. An adult cardiac clinic was started in 1912 by Dr Joseph H. Pratt and this too was subsequently taken in charge by Dr. White.

The publication by Miss Tyng of the results of the Bellevue study aroused great interest among a number of New York physicians and this was intensified when Dr. Haven Emerson, then Commissioner of Health, secured figures indicating that there might be as many as 20,000 children with heart disease in the public schools. During the winter of 1915-16 discussions and conferences were held in the home of Dr. Walter B. James to determine how the number of cardiac patients might be determined and what measures could be taken to help them. It was partly a realization of the lack of accurate information relating to heart disease which

led to the formation of the Association for the Prevention and Relief of Heart Disease at the home of Dr James on May 2 1916 Among those taking an active part in the organization and subsequent work of this Association were Drs W B James T B Barringer L A Conner Warren Coleman N L Deming Haven Emerson R H Halsey T Stuart Hart and Alexander Lambert Miss M L Woughter was selected as Executive Secretary and an office was provided by the Burke Foundation in connection with its own offices in East 57th Street The objects and purposes of the new Association were stated as follows To gather data from wide sources and arrange for its practical application in education occupation and social welfare to study and develop occupations and vocational guidance for cardiacs in standard trades and situations as well as in special lines is already begun to take a formative interest in workmen's compensation insurance and similar problems affecting cardiac patients to assist in the formation of more cardiac classes in appropriate districts and to extend and correlate their efforts to work constantly for the prevention of heart disease through the dissemination of information and the application of preventive means (as in increased facilities for post-rheumatic throat and dental treatments) to organize cardiac convalescence to provide larger opportunities in existing institutions especially for youth to assist in coordinating the various efforts in this field as made by health departments schools cardiac classes special investigators the Trade School for Cardiacs etc and to encourage the formation of branch associations

The first endeavor of the Association was to encourage the formation of cardiac classes in other hospitals and outpatient departments similar to the one at Bellevue The suggestion was received so cordially that within a short time 20 clinics had been formed and these continued to function through the period of the war (1917 to 1919) when the activities of the parent Association were temporarily suspended Almost as soon as clinics began to function it became apparent that there was urgent need for standardization of methods and nomenclature and as early as February 1917 an Association of Cardiac Clinics was formed for this purpose This was an independent organization until February 1923 when it became a committee of the Association for the Prevention and Relief of Heart Disease It is interesting to observe that within about two months of its formation the Association of Cardiac Clinics had

developed a system for classification of cardiac patients. The following scheme from which the modern classification has grown was adopted on April 30, 1917:

ALL CLINICS USE A COMMON STANDARD FOR CLASSIFYING CASES

- I Organic (symptoms of insufficiency never evident)
- II Organic (symptoms of insufficiency in the past, not present)
- III Organic (symptoms of insufficiency present)
- IV Possible Heart Disease (doubtful murmurs, mainly functional, possibly organic)
- V Potential Heart Disease (predisposing history)

Within a short time this was found to be unsatisfactory, and on February 2, 1921, the Association of Cardiac Clinics altered it to the following:

THE FUNCTIONAL CLASSIFICATION OF CARDIAC PATIENTS

- Class I Patients with organic heart disease who are able to carry on their habitual physical activity
- Class II Patients with organic heart disease who are able to carry on diminished physical activity
 - (a) Slightly decreased
 - (b) Greatly decreased
- Class III Patients with organic heart disease who are unable to carry on any physical activity
- Class IV Patients with possible heart disease. Patients who have abnormal physical signs in the heart but in whom the general picture or the character of the physical signs leads us to believe that they do not originate from cardiac disease
- Class V Patients with potential heart disease. Patients who do not have any suggestion of cardiac disease but who are suffering from an infectious condition which may be accompanied by such disease, e. g., rheumatic fever, tonsillitis, chorea, syphilis, etc.

It may be noted in passing that this classification was adopted throughout the United States within a few years and remained in general use until 1939, when a slightly different one was recommended by the Criteria Committee of the New York Heart Association and adopted by the American Heart Association.

The accomplishments, problems, and aims of the Association for the Prevention and Relief of Heart Disease and of the Association of Cardiac

Clinics were made known to large numbers of physicians attending the annual sessions of the American Medical Association with the result that requests for information and assistance began to come in increasing volume from cities all over the United States. By 1922 the interest of other cities was so apparent that it seemed proper to consider the possibility of creating a body of national scope. In April of this year invitations were sent by the New York group to approximately 100 physicians from all parts of the country to meet at the Hotel Claridge in St. Louis, Mo. on Wednesday, May 24, 1922, at the time of the annual session of the American Medical Association. Forty six accepted the invitation and under the chairmanship of Dr. Robert H. Halsey, discussed the necessity for a new organization.* A tentative plan drawn up by the New York group was presented by Dr. Haven Emerson and was discussed by Dr. Herrick, President of the Chicago Association, Dr. Sailer, President of the Philadelphia Association, Dr. Paul White, Chairman of the Boston Association of Cardiac Clinics, Dr. Thayer of Baltimore, and others. When it was clear that the sentiment of the meeting was in favor of proceeding with the formation of a national body, the chairman of the meeting was empowered to appoint a committee of five men to proceed with the details of organization. The committee as appointed consisted of Dr. Lewis A. Conner, Chairman and Drs. James B. Herrick, Hugh McCulloch, Joseph Sailer, and Paul D. White with Dr. Robert H. Halsey as a member *ex officio*.

The committee selected the name American Heart Association because of its brevity and also because it included Canada, Central America, and South America. It was decided to incorporate under the Membership Corporations Law of New York State. Informal conferences with mem-

* The available records indicate that the following were among those who attended this meeting:

Dr. Alexander Lambert
Dr. W. S. Thayer
Dr. W. A. Rupe
Dr. Neuton S. Stern
Dr. J. E. Benjamin
Dr. A. D. Kaiser
Dr. Fred M. Smith
Dr. W. Dickenson
Dr. T. Homer Coffen
Dr. S. dney Strauss
Dr. F. A. Willis
Dr. Merrill M. Myers
Dr. H. E. B. Pardee
Dr. Hugh McCulloch

Dr. J. B. Herrick
Dr. Joseph Sailer
Dr. Robert C. Giles
Dr. Harvey M. Ewing
Dr. John Ackman
Dr. Drew Luten
Dr. E. F. Horine
Dr. S. C. Smith
Dr. John Wyckoff
Dr. H. E. Mock
Dr. Cary Eggleston
Dr. Robert B. Preble
Dr. W. F. Watton
Miss H. E. Heikes

Dr. Robert H. Halsey
Dr. Paul D. White
Dr. Wm. H. Deaderick
Dr. Arthur E. Strauss
Dr. William D. Stroud
Dr. J. V. Greenebaum
Dr. Louis F. Bishop
Dr. James E. Talley
Dr. W. W. Hamburger
Dr. John Phillips
Dr. Walter L. Berning
Dr. N. C. Gilbert
Dr. Haven Emerson
Miss M. L. Woughter

bers from various cities were held during the annual session of the American Medical Association in 1923 and on March 14, 1924, the Certificate of Incorporation was drawn up and signed by Drs Robert B Preble, Joseph Sailer, Paul D White, Hugh McCulloch, Robert H Halsey, and Lewis A Conner. The Certificate was approved on May 14, 1924, by the Commissioner of Education Mr F P Graves, and on May 20, 1924, by Supreme Court Justice Geigerich. This official permission for a national organization was presented at the meeting of the American Medical Association in Chicago. On June 10, 1924, the formality of organization was completed by election of the first Board of Directors and the election by this Board of the first officers and the Executive Committee, to hold office until the first annual meeting in February, 1925. The officers were: President, Dr Lewis A Conner, Vice President Dr James B Herrick, Secretary, Dr Robert H Halsey, Treasurer, Dr Paul D White. The Executive Committee consisted of Dr T Stuart Hart, Chairman, and Drs Haven Emerson, Joseph Sailer, William D Stroud, William H Robey, and the President and Secretary.*

The purposes of the American Heart Association as set forth in the Certificate of Incorporation are: The study and the dissemination and application of knowledge concerning the causes, treatment, and prevention of heart disease, the gathering of information on heart disease, the development and application of measures that will prevent heart disease, search for and provision of occupations suitable for patients with heart disease, the promotion of the establishment of special dispensary classes for patients with heart disease, the extension of opportunities for adequate care of cardiac convalescents, the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated for self support, and the encouragement and establishment of local associations with similar objects throughout the United States. It is specifically stated that 'nothing in the foregoing objects and purposes is to be construed as giving the corporation authority for the conduct of a dispensary or institution of a charitable, eleemosynary, correctional, or reformatory character.'

* The 15 Directors elected at this meeting were: Dr Joseph Sailer, Dr George W Norris and Dr William D Stroud, Philadelphia; Dr James B Herrick, Dr Robert B Preble and Dr Sidney Strauss, Chicago; Dr Paul D White, Dr Henry Jackson and Dr William H Robey, Jr, Boston; Dr Haven Emerson, Dr Robert H Halsey, Dr T Stuart Hart and Dr Lewis A Conner, New York City; Dr Charles J McIntyre of Indianapolis and Dr Hugh McCulloch of St. Louis.

Eight years after its formation a more specific program for the guidance of the Association was prepared by a large committee under the wise leadership of Dr John Wyckoff. This was published in the Bulletin of the Association for July 1939 and the following abbreviated version will indicate its general nature.

The general purposes of the American Heart Association shall be to increase the knowledge and stimulate interest in diseases of the heart and to promote agencies for the prevention and care of this class of disease. To accomplish this the Association is interested in the following:

- (1) The continued improvement of the central organization and its maintenance at a high level of efficiency.
- (2) continuing and amplifying the educational activities of the Association by the preparation, publication and distribution of books, pamphlets and abstracts bearing on the subject of heart disease.
- (3) fostering the establishment of local heart associations in cooperation with the organized profession and whenever possible with existing health organizations.
- (4) promoting the establishment of additional efficient cardiac clinics where needed and encouraging the maintenance of all clinics at the highest possible efficiency.
- (5) developing adequate hospitalization for cardiac patients during the stage of infection or heart failure, whether such condition be temporary or permanent.
- (6) encouraging the development of convalescent care for patients with diseases of the heart by developing additional institutions by disseminating knowledge concerning methods of handling patients convalescent from heart failure and infection and by fostering the development of a program of convalescent care in the home.
- (7) a consideration of the need of sanatorium care for cardiac patients with active rheumatic fever.
- (8) development of a policy as to the best management of children of school and preschool age who have diseases of the heart.
- (9) efforts to develop economic independence when possible among patients with diseases of the heart by means of occupational therapy, vocational guidance, trade schools and the development of interest among bureaus and agencies for the handicapped.
- (10) the development of graduate instruction.
- (11) the promotion of investigations.
- (12) increasing the funds of the Association for general purposes, for specific projects and for endowment by means of increasing its membership and by solicitation of individuals and foundations.

A few of the more important landmarks in the development of the Association after 1904 may be mentioned briefly. In May 1925 there was authorized the publication of a Bulletin which should be essentially a news vehicle for the information and guidance of interested groups. For some years this was published bimonthly but was then changed to a quarterly publication. In the same year a committee was appointed under the chairmanship of Dr William D. Stroud to consider the matter of a standard nomenclature for diseases of the heart. After many conferences a nomenclature was approved by the Association and published in the *American Heart Journal* of December 1926. By 1928 the Criteria Committee of the New York Heart Association (then the Heart Committee of the New York Tuberculosis and Health Association) composed of Drs Joseph H. Bunton, Robert L. Levy, W. C. Munly and Harold E. B. Pardee had prepared a book entitled *Criteria for the Classification and Diagnosis of Heart Disease* which was approved and adopted by the American Heart Association. This splendid book is now (1940) in its fourth edition, has been steadily improved and enlarged and has had a wide and beneficial influence upon the education and practice of physicians throughout the country. The American Heart Association has acted as the distributor of this volume from the very beginning and cooperated in the publication of the first three editions. The title of the current edition has been altered to *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*.

In May 1905 the Association authorized the publication of a special journal for the presentation of papers relating to diseases of the heart and the first issue of the *American Heart Journal* appeared in October 1905 under the editorship of Dr Lewis A. Conner. For the first ten years it was published bimonthly but in 1936 it became a monthly journal. From the very beginning Dr Conner insisted that the *Journal* must be under the editorial supervision of the American Heart Association and he often consulted the Directors about various matters. It was not until some years later however that formal agreements were concluded which made the *Journal* the official organ of the Association and under its direct editorial control. Under the editorship of Dr Conner and Dr Hugh McCulloch the *Journal* became and has since remained the leading journal of the world in its special field. In 1936 Dr Conner resigned as editor and was succeeded by Dr Fred M. Smith.

In January, 1932, there appeared the first issue of a special leaflet authorized by the Association in response to many requests. This was known as "Modern Concepts of Cardiovascular Disease," and has been published monthly for eight years. With a few exceptions, each number has consisted of an entire article written especially for the *Concepts* by some eminent authority invited by the editor. The object of these leaflets was to keep practicing physicians informed of current advances and developments in the cardiovascular field, and especially to present them regularly with authoritative reviews of the available knowledge respecting important and practical aspects of diagnosis, prognosis, and treatment.

A most important change in the fundamental nature of the Association took place in 1936, when a Section for the Study of the Peripheral Circulation was added. For several years preceding this it was realized that interest in the physiology and diseases of the vascular system was increasing very rapidly, and it seemed clear that a society would soon be formed by those who were actively working in this field. It was the belief of the majority of both the "heart specialists" and the "vascular specialists" that the study of the heart and of the peripheral circulation should not be separated, since they represented two integral parts of one system. After many conferences, a large group of men interested in the study of the peripheral circulation organized as a Section of the American Heart Association, becoming an important part of the older organization but with their own officers, committees, and by-laws. At the same time, partly because of the requirements of this added Section and partly in response to widespread criticism, the number of Directors of the Association was increased from 15 to 25 (later modified to read "not less than 25 and not more than 30"), and the Section for the Study of the Peripheral Circulation was given appropriate representation on the Board. Representatives of this Section were added to the editorial board of the *American Heart Journal*, and Dr. Irving S. Wright became an Associate Editor in charge of the papers relating to vascular disease and physiology. In January, 1936, the *Journal* became a monthly instead of a bimonthly publication in order to provide space for the increasing number of excellent contributions and for articles relating to the peripheral circulation.

In May, 1937, the first international radio broadcast devoted to health was arranged and sponsored jointly by the American Heart Association

and Irvington House (a convalescent hospital for cardiac children at Irvington-on-Hudson, N. Y.). The National Broadcasting Company generously gave their services and facilities without charge. The general subject of the half-hour program was "Rheumatic Heart Disease in Childhood," and the speakers included Lord Horder, who spoke from England, Dr. William J. Kerr (then President of the Association), who spoke from San Francisco, Dr. Homer F. Swift of New York, and Dr. T. Duckett Jones of Boston. The commentator was Dr. Howard Haggard of New Haven.

In 1937, in response to a steadily growing demand, the Association appointed a committee of distinguished investigators and clinicians to study the confused situation that had been created by the introduction of a precordial lead into clinical electrocardiography a few years earlier. There was no uniformity of procedure or nomenclature, and it was becoming increasingly difficult to interpret and appraise the results reported by different observers. The Committee appointed for this study consisted of Dr. Frank N. Wilson, Chairman, and Drs. Arlie R. Barnes, Harold E. B. Pardee, Paul D. White, and Charles C. Wolferth. Their work was done in close coöperation with a corresponding committee of the Cardiac Society of Great Britain and Ireland, which included Drs. D. Evan Bedford, John Cowan, A. N. Drury, I. G. W. Hill, John Parkinson, and P. H. Wood. After some months of meetings and correspondence it was possible to arrive at conclusions which were acceptable to the full membership of both Committees. These were published under the title "Standardization of Precordial Leads: Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland" in the *American Heart Journal* and *Journal of the American Medical Association* early in 1938, and simultaneously in the *British Medical Journal* and the *Lancet*. After the lapse of two years it is possible to add that the recommendations of this report were widely accepted by investigators and practitioners, with the result that almost complete uniformity of procedure has been secured.

This matter is mentioned at some length because of its implications. The results achieved by this committee indicated clearly that order could be brought out of chaos if a national organization would sponsor the necessary action and would work through a group of men whose knowledge and standing could not be questioned. But they also revealed the

possibility of harmonious and helpful coöperation between the two great English-speaking nations in matters of scientific interest and importance.

About a year and a half later a similar procedure was followed with respect to the standardization of blood pressure readings. Investigations by Dr. Irving S. Wright and his coworkers had revealed a surprising lack of uniformity in the teaching of medical students and in the procedures employed by practicing physicians with respect to the determination of the blood pressure. A committee was appointed by the American Heart Association, composed of Dr. Irving S. Wright, Chairman, and Drs. M. H. Barker, Joseph Erlanger, Jonathan Meakins, Ralph Schneider, S. B. Scholz, Jr., Harry Ungerleider, Paul D. White, and Carl Wiggers. This group worked in close coöperation with a committee appointed for the purpose by the Cardiac Society of Great Britain and Ireland, consisting of Dr. Maurice Campbell, Chairman, and Drs. Crichton Bramwell, T. F. Cotton, William Evans, A. R. Gilchrist, and John Hay. There were only one or two minor differences of opinion between the two committees, and a joint report was again published simultaneously in the two English and two American journals mentioned above. This appeared in July, 1939, under the title "Standardization of Blood Pressure Readings: Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland."

ACTIVITIES OF THE ASSOCIATION

The general nature of the work performed by the Association has been indicated to some extent in the preceding pages. It may be defined broadly as educational: the collection, correlation, and distribution of all types of educational and informational material relating to the normal and abnormal heart and vascular system. Its educational efforts extend in many directions, but in recent years have applied more to physicians than to laymen, partly for the reasons stated in the earlier pages of this chapter. No attempt will be made to give a comprehensive list of the past and present activities of the Association, but a few may be cited as illustrative.

Meetings: It holds an annual scientific meeting lasting two days, just prior to the annual session of the American Medical Association. On one day the program is composed of papers relating primarily to the heart; on the other, to papers concerned mainly with the peripheral

that they have been an important contribution to the special education of the practicing physician

The relation of the Association to the *American Heart Journal* has been mentioned briefly above

In addition to its own publications the Association acts as the national distributor for the invaluable *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*, prepared by the Criteria Committee of the New York Heart Association. The fourth edition which appeared in 1939 is a noteworthy achievement and has been accorded great praise

Other Educational Activities Another type of educational activity consists of the preparation and distribution of such material as drawings of the heart, charts, lantern slides, silent films, sound films, models of the heart in health and disease, outlines of lectures, printed forms for use in cardiac clinics, and pamphlets relating to various aspects of heart disease. Most of this material is prepared in response to numerous requests, usually by one of the subcommittees of the Committee on Education and Publicity or by some other eminently qualified authority selected by them. There is a wide, constant, and growing demand for all this material, and for much that is not yet available. Much of the printed matter is distributed free; lantern slides, films, and models are rented for a nominal fee or sold.

Clinics Approximately 70 cardiac clinics or heart associations are affiliated members of the Association. Standards for the organization and conduct of such clinics have been established by the Association, and no clinic is accepted into membership unless its personnel and the character of its work fulfill these standards. Regular reports are received from the clinics, and a renewal application is filed each year. Efforts are made to maintain a high level of efficiency in the work of the clinics and to encourage the formation of new clinics in localities where they are needed.

Similar standard requirements for the organization and functioning of vascular clinics have recently been completed by the Vascular Section of the Association, and it is hoped that many such clinics will soon be admitted to affiliated membership.

In addition to the specific activities mentioned above, there are literally hundreds of problems and questions presented annually by members, clinics, hospitals, other heart associations, authors of books or

magazine articles who desire authoritative information, book publishers, manufacturers, local or State health officers, welfare departments, social workers, nurses, teachers, and many others. Every question receives careful consideration and answer; if it is of sufficient importance, it is referred to the proper committee or to the Board of Directors.

METHOD OF WORK

It has been clearly implied in the foregoing pages that the work of the Association is accomplished largely by means of committees appointed annually. Many of these serve continuously, with changes in their membership every year or two, while others are appointed for special purposes and are disbanded upon accomplishment of their work. The final authority rests in the Board of Directors; this consists of not less than 25 and not more than 30 directors who are elected by ballot of all the members. The United States and Canada are divided into five geographical regions, each of which must have four representatives on the Board; in addition, the four officers and the editor-in-chief of the *American Heart Journal* are directors *ex officio*. The Board usually meets at least twice annually, but throughout the year various matters are placed before the members by mail. The Executive Committee of the Board, which consists of ten members appointed by the President, meets at more frequent intervals whenever the amount or importance of accumulated material necessitates it.

A list of the present Directors and of the various committees is given below. It should be noted, however, that the personnel changes to some extent every year, and this list is correct only for the year 1910.

In connection with the publication of this list, the present writer cannot refrain from adding a more personal word. It has been my privilege for the past few years to act as the Executive Secretary of the Association and as Chairman of its Executive Committee; the contributions of the men named below and of their predecessors are probably better known to me than to any other one person. It would be impossible adequately to praise the magnificent spirit displayed by these scores of busy, eminent men, who give freely of their time and thought with no remuneration other than their consciousness of helping a worthy cause in which they are interested. Members of the Board and of various committees often travel long distances in order to attend meetings in New York, even though they must pay all their expenses to do so. They cheerfully accept

tedious assignments that require weeks or months of hard work for their completion. Their attitude is wholly idealistic, I have never known in any other group such complete absence of all thought of self and of personal reward. Much of the most important and time-consuming work of the Association is done by men whose contribution remains unknown except perhaps to the members of the Executive Committee. Even in the medical profession, with its glorious tradition of unselfish service, it must be rare indeed to find a large group so unified in spirit, so willing to give much and ask nothing in return, so earnest in considering the welfare of others and the best means of promoting it. If the American Heart Association has grown in size and in helpful influence, it is largely because of the continuous and unselfish devotion that has characterized the attitude of its officers, directors, and committee members. It is a privilege to pay them the tribute of this brief and inadequate word of praise.

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1927 1928	Dr James B Herrick	Dr William H Robey
1929 1930	Dr William H Robey	Dr Haven Emerson
1931 1932	Dr Robert H Halsey	Dr Robert S Preble
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1935 1936	Dr John Wyckoff	Dr William J Kerr
1937 1938	Dr William J Kerr	Dr William D Stroud
1939 1940	Dr William D Stroud	Dr Paul D White

AIMS

Those who direct the work of the Association hope that it may ultimately meet more adequately the challenge of cardiovascular diseases, especially of those which cripple or kill children and young adults. The possibilities are too vast in number and scope to justify any extended consideration but a few words may be said in conclusion about several immediate objectives that should not long prove unattainable.

Every physician in this country who is really interested in diseases of the cardiovascular system and whose financial state permits it should be a member of the Association and a subscriber to the *Journal*. A considerable increase in membership would automatically enable the Association to extend its activities.

A full time travelling representative, preferably a physician should be available for visiting the affiliated clinics, hospitals, and heart associations keeping them fully informed of developments elsewhere helping to solve problems relating to management and methods increasing the interest of physicians and social workers and developing a closer and

more fruitful relationship between the central association and its scattered component members

The number of educational units —pamphlets, slides, charts, films, models, books, etc—should be increased and their quality constantly improved

Funds should be available for the furtherance of investigative work in the field of cardiac or vascular diseases, either by members and committees of the Association or by other qualified individuals or groups

The number of efficient cardiac clinics should be increased greatly

The Association should be in position to give not only encouragement and advice, but also practical aid in the establishment of convalescent homes and special cardiac hospitals

It should play the leading rôle in this country in improving the diagnosis and care of patients who have cardiovascular diseases and in raising the standards of cardiovascular practice in hospitals, clinics, offices, and homes

It should be the headquarters and the clearing house for every conceivable kind of information relating to cardiovascular disease especially that dealing with treatment and prevention, and there should be adequate facilities for distributing this information to all who need or desire it.

CHAPTER XXXIII

THE CARDIAC IN INDUSTRY

By WILLIAM D. STROUD, M.D.

Owing to the results of the World War, organization for training the handicapped and placing them in industry of necessity has progressed much more rapidly in Europe than in this country. In most European countries during the past 20 years, it has become a national obligation. In Germany they have gone so far as to regulate legally the training and placing of the handicapped, demanding that two per cent of all positions in various industries must be filled with individuals at least 50 per cent disabled. I first became interested in this problem while working in England during the years 1919 and 1920. One day at luncheon, Sir Thomas Lewis remarked that 'in the ideal State, no position in industry which might be filled by a person handicapped with cardiovascular disease should be filled with an entirely healthy individual. This of course is a strong statement but it certainly is worthy of careful consideration.

Most of the handicapped who may be rehabilitated and placed in industry are those with cardiovascular, arthritic and orthopedic disabilities. Various studies of the numbers of handicapped individuals and vital statistics would suggest that by far the largest group of such handicapped individuals trainable and available for industry is the cardiovascular group.

One of the first and most practical steps in planning for the training and placement of those handicapped with cardiovascular disease was the advocacy of a functional classification of cardiac patients that might be practical from the standpoint of the social service worker, those administering state and city rehabilitation bureaus and employers in industry. The Criteria Committee of the New York Heart Association has recommended the following functional classification of patients with organic heart disease ¹

Class I Patients with a cardiac disorder without limitation of physical activity. Ordinary physical activity causes no discomfort
(1048)

Class II Patients with a cardiac disorder with slight to moderate limitation of physical activity Ordinary physical activity causes discomfort

Class III Patients with a cardiac disorder with moderate to great limitation of physical activity Less than ordinary physical activity causes discomfort



FIGURE 1 A.L. aged nine years Home education Rheumatic fever (arthritis) enlargement of the heart mitral stenosis and insufficiency sinus arrhythmia Class III This little girl went to school for only two days Later she was taught in the Children's Heart Hospital She was not able to return to school and when the visiting teacher made her first contact she found a nine-year-old child who could read only at the first grade level and could not do better than 2A work in any subject She had a great fear of returning to school because she was so far behind In five months she has completed a year's work in the fundamental subjects and looks forward with pleasure to returning to school next September Referred by Philadelphia Heart Association (Courtesy Shuntz Society)

Class IV Patients with a cardiac disorder unable to carry on any physical activity without discomfort

The greatest difficulty in planning for the training and placement of those handicapped with cardiovascular disease is the fear in the minds of the employers as to the result of the workmen's compensation act and

the possibilities if cardiac patients are given work and later break down in their employ. It is notoriously difficult to state positively that almost any occupation may not have contributed to some slight degree to the progression of the cardiovascular lesion that has finally ended in heart failure or sudden death.

During the past few years I have given expert testimony in such cases before a compensation board referee and I have been impressed with the marked difference in various States as to the standards on which compensation board referees make their decisions as to the relationship of cardiovascular disease to sudden death. In Pennsylvania a man while filling a bucket at a marble hopper suddenly fell, striking his head on the edge of the marble hopper. He died within a few minutes and the coroner's diagnosis as to the cause of death was coronary thrombosis. The family was awarded compensation for accidental death since the referee decided that if the man had struck his head against the marble hopper as he fell the coronary thrombosis might not have killed him!

In the District of Columbia a man who for many years had placed fruit on a display stand of a fruit store and piled potato sacks in a corner developed a pain in his chest while lifting one of the potato sacks. He went to bed. A few days later he developed evidence of congestive heart failure. A physician examined him and found a plus four Wassermann reaction, evidence of syphilitic cardiovascular disease with aortic insufficiency and congestive heart failure. Six months later the patient died never having sufficiently recovered to arise from his bed. The referee awarded compensation to the family since he decided that the lifting of the potato sack was a contributing factor in the development of the heart failure in spite of the fact that his work the day of the so-called accident was no different than on any other day during the past few years.

In West Virginia a mule driver in a mine helped his mule by pushing a small coal car over a small incline. A few minutes later he developed an agonizing epigastric and anterior chest pain. He died a few minutes later and the coroner's diagnosis as to the cause of death was coronary thrombosis. The compensation board referee decided against awarding compensation to the family since helping the mule at times was part of his ordinary duty in the place where he worked.

Until there is some uniformity in the workmen's compensation acts in the various States and some uniformity in the interpretation of the

acts by the various referees and courts, it will be a difficult matter to persuade employers to accept individuals handicapped by cardiovascular disease.

During the past 21 years the medical profession has learned that in spite of valvular disease, many individuals can perform the average type of work without materially impairing their health or shortening their lives. We know today that unless an individual is in a state of borderline cardiac failure, moderate physical effort appears to play little part in the



FIGURE 2 W. C. C. aged 60 arteriosclerosis cardiac enlargement and coronary sclerosis normal sinus rhythm Class III This man was a World War veteran and was unable to procure employment for many years. He had vocational training at home for several years before his death. The occupational therapist trained him to make hooked rugs. He became quite an expert at this and the organization was able to dispose of them for him. (Courtesy Shut-in Society.)

progression of the disease or in the production of congestive heart failure. Certainly, sedentary occupations even if they may demand unusual mental concentration or nervous and muscular coordination do not seem to hurt the average patient with rheumatic valvular heart disease unless hypertension is present. In cases of hypertension or of coronary insufficiency, of course, it is a different story, but even here many individuals even though they may have had a cardiac infarct, can carry on sedentary occupations which do not entail much mental concentration nervous tension or physical effort. Too often physicians advise patients with coronary insufficiency with or without hypertension or healed cardiac infarcts, to give up a lucrative position in which the patient might have carried on for many years upon a restricted mental and physical duty.

routine. The realization by the medical profession that infections appear to play a larger part in cardiac failure and the progression of cardiac disease than does physical effort should aid in the placement of cardiac patients in industry if this impression through public health education can be passed on to the employer and the general public.

The placement of cardiac patients in suitable employment was carried on successfully from 1906 to 1932 by the Philadelphia Heart Association through a cooperative arrangement with the Philadelphia Health Council and Tuberculosis Committee.²

During the seven years from 1906 through 1932 a total of 280 heart patients were placed in employment, some of them more than once, so that a total of 388 jobs were filled by these patients. During the first three years of this service no effort was made to ascertain the amount earned by the cardiac patients who were placed, but from the year 1929 to 1932 the earnings of heart patients placed by the service amounted to upwards of \$90,000.

The applicants for placement were referred from the 21 heart clinics of Philadelphia and by private physicians. Each applicant had a medical examination and a diagnosis card filled out by the referring physician. The diagnosis included etiologic, anatomic and physiologic factors, a functional classification and an indication of the work tolerance of the applicant in terms of the activities he normally would undertake. In addition to this report each applicant was studied individually by the social service worker in charge of this placement service as to his employment history, his mental attitude and his abilities as a worker. Each presented an individual problem.

Finding employment for the applicants required persistent interviewing of employers. All sections of the city were included so as to place the applicants in work near their homes and reduce travel if possible. In order to get an idea of safe jobs in factories as well as of the physical conditions existing in the plant, visits were made to various parts of the plants.

Few employers desire persons below par physically, even for the simplest jobs. All placement work of handicapped persons requires persistent solicitation of the employers. They must be told that persons whose physical condition has been determined by an examination can be placed in suitable work and prove to be a definite asset. It is pointed out

also that physically handicapped workers when properly placed are usually permanent and faithful since they appreciate having a job. The fact that a continuous follow up after placement is stressed which insures that the worker will not be allowed to remain on the job unless he can safely do so is pointed out. Often after a handicapped person has been placed and proves to be a successful worker calls are made for another handicapped worker.

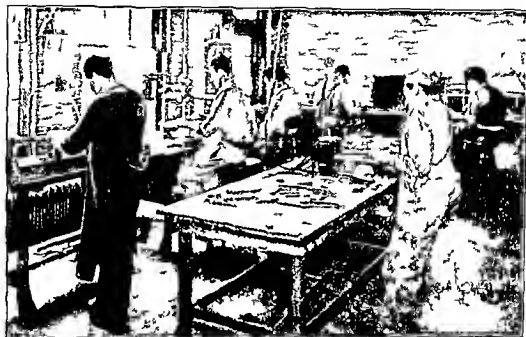


FIGURE 3 N. D. aged 19 died of fever cardiac enlargement and mental inefficiency normal sinus rhythm. Chris H. Began working in the food working for a time seven hours a day October 31 1931 at \$ a week. Total wages \$ 3.58. Total time worked three months. This was the only place employed in his life. He is very eager to work even though it is not possible to pay him a larger salary. He is very much interested in the work and did it very well. (Courtesy S. I. T. N. Society.)

A single illustration from the records of this service shows the value of this work. Rocco C. is a boy who had started to learn the plumber's trade. As it involved a great deal of physical strain which was showing its effect on his damaged heart his physician insisted that he give it up. After Rocco had been seen and some idea of his capabilities had been obtained he was sent to talk with the superintendent of a leather goods factory. This factory makes high grade leather purses handbags and toilet cases. Although the superintendent had said he would not be able to take on any beginners then after talking with Rocco he employed him to begin the following day. Since then Rocco has had his troubles

at home, as his father was out of work for some time, and much pressure was brought to bear to make him leave and get a job paying more money. This, however, he refused to do. Rocco has since had a raise, and the superintendent reports that he takes an interest in his work and is getting along nicely. Rocco's frequent correspondence corroborates this. His physical condition is satisfactory as reported by the clinic physician.

TABLE I
VOCATIONAL POSSIBILITIES FOR HEART PATIENTS

<i>Skilled Labor</i>	
Woodwork	Electrical Construction
(a) Cabinetmaking	(a) Wiring signs
(b) Novelty—small toys jigsaw puzzles bag tops small frames	(b) Radio work
	(c) Assembling electric cords and the like
Textiles	Mechanical Drafting
(a) Chemistry	(a) Making and filing blueprints
(b) Weaving	(b) Architectural planning
(c) Designing	
Commercial Work	Commercial Art
(a) Stenography and typewriting	(a) Advertising
(b) Filing and indexing	(b) Postermaking
(c) Telephone operator	
Handiwork	Designing
(a) Basketry and caning	(a) Jewelry
(b) Fine sewing	(b) Clothes
(c) Quilting	(c) Wallpaper linoleum
(d) Hooked rugmaking	Vocational Music
(e) Leather art	(a) Playing an instrument
(f) Monogramming	(b) Teaching an instrument
(g) Embroidery	Librarian (no lifting of heavy books)
Jewelry	Dressmaking
(a) Polishing	Millinery
(b) Engraving	Hairdressing
(c) Filing	Tailoring
(d) Soldering	Shoe Cobbling
(e) Carding	Necktie Cutting
<i>Unskilled Labor</i>	
Factory Work	Errand boy
(a) Packing and dressing dolls painting faces making dolls clothes	Office boy
(b) Lining trays and drawers riveting small parts in trunk factory	(a) Stamping
(c) Stripping and packing tobacco	(b) Labeling
(d) Finishing running ribbons packing in garment factory	(c) Sorting slips
(e) Packing in any factory where objects handled are not heavy	(d) Folding posters
	Clerical work filing
	Kitchen work in hotels

In the study of employment possibilities for the physically handicapped in Philadelphia industry, the occupations suitable for general cardiac patients have been defined by the following restrictions:

Generally good working conditions as to ventilation and comfort, without special hazard of materials, machinery, electricity and so on

TABLE II
POSSIBILITIES FOR EMPLOYMENT OF CARDIAC PATIENTS IN
PHILADELPHIA INDUSTRY

<i>Industry</i>	<i>Probable Number per 1000</i>	<i>Normal Employment</i>	<i>Number of Cardiac Patients Employable in Normal Times</i>
Storage battery manufacturing	36	4,000	232
Radio set manufacturing	697	13,200	9,200
Hat and cap manufacturing		8,000	
Glass manufacturing and processing	111	1,200	173
Milk distribution	28	4,000	112
Ball bearing manufacturing	161	1,100	290
Knit goods manufacturing	215	6,000	1,170
Hosiery manufacturing	230	18,000	1,110
Garage service	680	5,000	9,100
Machine tool manufacturing	133	2,000	870
Printing and publishing		12,000	
Drug manufacturing	678	1,000	678
Paper manufacturing		1,000	
Recording instrument manufacturing	816	1,500	1,209
Leather tanning and dyeing		3,000	
Gear manufacturing	268	500	131
Mail order industry	218	3,000	714
Cigaret and cigar manufacturing	1	6,100	6
Paint manufacturing		2,000	
Sugar refining	392	1,100	131
Shoe manufacturing	153	3,100	336
Bakery industry	329	6,000	1,932
Confectionery manufacturing	506	3,200	1,619
Sporting goods manufacturing	916	600	568
Laundry industry		5,000	
		113,300	27,761

These are separated into six classes
For 1000 in each class the figures are

Men—

Novice	310	9,600	2,976
Trained	159	16,200	2,576
Skilled	141	15,000	6,180

Women—

Novice	479	7,900	3,781
Trained	270	22,800	6,156
Skilled	193	11,900	5,699

Light work requiring no rapid movements of the body

A minimum of nervous tension such as may be attendant on intensive production methods or the operation of high speed machinery

During the years 1934 and 1935 Mr F W Steiber, working for the Philadelphia Branch of the Pennsylvania State Bureau of Rehabilitation made a study of the employment possibilities for the physically handicapped



FIGURE 1 J. T. a cardiac patient engaged in machine and fine hand sewing. Referred by the Pennsylvania Hospital. Rheumatic fever, cardiac enlargement, mitral insufficiency, mitral stenosis, regular sinus rhythm, Class I. She has worked regularly in the shop for eight years with very little loss of time because of illness. Her health has steadily improved. (Courtesy Shut-in Society)

employed in Philadelphia industry. In the pursuance of this study 10,000 workers have been more or less directly observed in the performance of 1,000 different operations in 25 industries. The data gathered during the study of these operations from the standpoint of performance of the specifically handicapped have been tabulated on the basis of possibilities per thousand workers in each industry. For the cardiac classification the data are given in Table II.

The large variations among the industries reflect primarily the difference in the character of the work. In some cases notably hat and cap

manufacturing the influence of a strict medical examination of employees is paramount. It must also be admitted that the individual making the study has had an influence in some cases though these men have all been engineers with industrial experience.

A number of other industries have been covered without tabulations having been made. The general showing bears out the figures of the tables indicating that 25 per cent of all jobs in industry are possible of performance by this class of handicapped person without compromising either the job or the jobholder.

TRAINING IN SHELTERED WORKSHOPS³

In the sheltered workshops of the Pennsylvania Branch of the Shut in Society, and Vocational Adjustment Service for the Handicapped from 1932 to 1940 there have been employed 28 persons with heart conditions classified from Class II to Class III. They worked at carpentry, machine and hand sewing, furniture repair and refinishing and general work about the place.

In the machine and hand sewing department there were ten who worked six hours a day. They were paid from 75 cents to \$1.68 a day and furnished milk for lunch. In the woodworking, upholstery and wheelchair departments 17 persons worked from three to five days a week from five to seven hours a day. One worked at part time cleaning. They received from \$1.00 to \$3.50 a day. These persons accomplished a good normal day's work in these departments. There were no deaths and no accidents while at work. In a year two persons, both women, fainted and were treated in the rest room. Of these 28 cardiac patients three have died as a result of their heart condition but this was at home under ordinary circumstances.

We have not been successful in placing any cardiac patients in industry through the Rehabilitation Bureau and this I believe is due largely to the unemployment situation that has prevailed for the past nine years.

CONCLUSIONS

1. Vital statistics suggest that individuals with cardiovascular disease comprise as large a group, if not the largest group, of persons with physical handicaps.

2. It seems questionable whether physical effort is responsible for the production of cardiovascular disease or plays as large a part in the

progression of cardiovascular disease as has been previously believed. If this is true, the training of cardiac patients and their placement in industry constitute as great a responsibility for the physician as any other form of therapeutics—in fact, in Class I and II cases a much more important responsibility than medication or other forms of therapy.



FIGURE 5. R. B. aged 50 years a cardiac patient engaged in woodworking. Rheumatic fever, mitral stenosis and insufficiency, normal sinus rhythm, Class II. He has worked in the shop steadily for eight years. (Courtesy, Shut in Society.)

3. With proper functional classification by private physicians or physicians in heart clinics, with especially trained placement workers in city and state rehabilitation bureaus, cardiac patients in much larger numbers than previously recognized may earn a living through training in shel-

tered workshops with ultimate placement in industry or if previously trained through direct placement in industry

4 If common labor is divided into two classes namely light labor and heavy labor almost 100 per cent of cardiac patients except those in Class IV are employable at light labor

5 To accomplish such rehabilitation and placements it is necessary to obtain the interest of the medical profession and to impress physicians with their responsibility toward the handicapped and the necessity of cooperating with the social service workers especially trained placement workers and city state and county rehabilitation bureaus Employers should be carefully approached and educated Finally and perhaps most important of all is the sympathetic handling of the unfortunate individual handicapped by cardiovascular disease

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CHAPTER XXXIV

CONGESTIVE HEART FAILURE

By ALBERT W. BROWER, M.D., and WILLIAM D. STROUD, M.D.

Definition: Heart failure is the inability of the heart muscle to maintain a circulation sufficient for the usual daily requirements of the body. When general venous congestion is present, the clinical syndrome is called congestive heart failure. It is important to distinguish between congestive heart failure and failure of the peripheral vascular system which occurs in syncope, shock or collapse. The latter has been freely covered in Chapter XLVI.

PATHOGENESIS AND MECHANISM

The cause of congestive heart failure is either an increase in the load of the heart or an impairment of the myocardium, or a combination of these two factors (which is the case in the great majority of instances). There is no pathological change which is characteristic of congestive heart failure, but, in all probability impairment of the myocardium almost always is a major etiological factor. The commonest structural abnormality is cardiac enlargement, which usually consists of hypertrophy and dilatation, but dilatation without hypertrophy is found in acute, rapid failure, such as may result from severe rheumatic carditis, coronary thrombosis or prolonged paroxysmal tachycardia. Dilatation rather than hypertrophy is responsible for most of the increase in size, especially of the largest hearts.

Hypertrophy is most generally regarded as the result of persistent increase in the energy expenditure of the heart. According to the "injury theory," proposed by Horvath⁷⁰ and supported by the experimental work of Eyster and his associates,^{30, 40} the fundamental cause of hypertrophy lies in an abnormal stretching of the muscle fibers which causes both work and hypertrophy. "Injury" may occur in the form of (a) strain in arterial hypertension, or a valvular or septal defect, (b) impaired nutrition in coronary artery disease or severe anemia, or (c) inflammation or toxicity in diseases, such as rheumatic fever, pneumonia and diphtheria.

In many instances, apparently more than one factor is active in the development of hypertrophy. But, in general, it seems that increased work plays a dominant rôle in the progression of hypertrophy, regardless of what the exact initiating influence may be.

The heart with healthy hypertrophied muscle is able to maintain an efficient circulation for many months or years in spite of an increased burden, such as arterial hypertension, or a valvular or septal defect. As a rule, pathological dilatation and failure do not occur until the muscle has been weakened through some injurious influence such as (a) impaired nutrition as in coronary artery disease and severe anemia (b) the inflammation and toxicity associated with acute diseases such as rheumatic fever, pneumonia and diphtheria or (c) fatigue (and the associated abnormal chemical state, particularly an excessive amount of lactic acid) arising from prolonged excessive rate in paroxysmal tachycardia, auricular fibrillation or auricular flutter. A structural defect such as a damaged valve tends to diminish the cardiac reserve and to hasten the onset of failure when weakening of the myocardium does set in. In many cases of essential hypertension with cardiac hypertrophy of long standing, congestive failure is entirely the result of the usual changes in the coronary arteries and the myocardium incident to advancing years. Occasionally, contrary to the general rule, a hypertrophied heart may fail entirely through the effort to overcome some extreme burden, without the presence of any degenerative or inflammatory change.

As a rule, the heart does not fail as a whole simultaneously. Through some particular strain or structural defect, one ventricle usually begins to fail before the other, and even when failure of both ventricles occurs the weakness of one may be predominant. Failure of the left ventricle occurs as a primary manifestation of myocardial insufficiency more often than does failure of the right ventricle in that the causes of left ventricular strain, namely, arterial hypertension, aortic valve disease and myocardial infarction are relatively commoner than mitral stenosis, chronic pulmonary disease and congenital pulmonary stenosis the causes of primary failure of the right ventricle. Actually, however, the commonest cause of failure of the right ventricle is insufficiency of the left ventricle and the resultant *back pressure* in the pulmonary vascular circuit.¹³⁷ As described by Hope⁶⁹ in 1832, 'When the distending pressure of the blood preponderates over the power of the (left) ventricle its contents

from not being duly expelled constitute an obstacle to the transmission of the auricular blood. Hence the auricle becomes overdistended and the obstruction may be propagated backwards through the lungs to the right side of the heart and there occasion the same series of phenomena. Thus the syndrome of congestive failure with general venous congestion is most commonly observed in clinical practice represents failure of both ventricles—failure of the right ventricle with systemic venous engorgement having been preceded by failure of the left ventricle (relatively a stage of symptoms rather than of signs) for a period usually of months or years.

The theory of back pressure appears more nearly correct than does that of forward failure in regard to the pathogenesis of the manifestations of congestive heart failure. According to the concept of forward failure the manifestations of failure arise from the diminished blood supply to the tissues which is the result of an inadequate cardiac output. The most striking example of the latter concept is observed in vascular collapse in which diminution in the volume of venous blood returning to the right auricle consequent to the fall in venous pressure occasions decrease in cardiac output. Occasionally in cases of marked aortic stenosis and failure of the left ventricle and also in acute cardiac collapse it does play a part particularly in the incidence of cerebral and coronary symptoms. At times the two types of failure coexist.

Occasionally the heart fails *as a whole* both ventricles being affected by some common strain such as rheumatic carditis, mitral regurgitation long continued, extremely rapid heart rates (as in auricular fibrillation, auricular flutter and paroxysmal tachycardia), thyrotoxicosis, severe anemia, dietary deficiency, myxedema, generalized coronary artery sclerosis and certain congenital developmental defects. Rarer causes of congestive failure are external pericardial adhesions, arteriovenous aneurysm, cardiac trauma, deformity of the thorax and neoplasms.

Acute cardiac failure may be observed in angina pectoris (accompanied by ventricular fibrillation or cardiac standstill), coronary thrombosis, pericardial effusion, paroxysmal tachycardia, complete heart block or diphtheritic myocarditis—with a clinical picture resembling that of peripheral vascular failure (shock, collapse) and accompanied by ashen pallor, cold clammy skin, weakness of the pulse and fall in blood pressure. But in the latter condition the veins are empty and the pulse rapid.

whereas in acute cardiac failure the veins may be distended and the heart rate slow

SYMPTOMS AND SIGNS

The cardinal symptom of myocardial insufficiency is dyspnea on exertion or at rest. With the exception of cases of sudden acute failure dyspnea usually is first experienced in the performance of some not unusual exertion and then as the degree of myocardial insufficiency increases it occurs with less physical effort until finally it is present even at rest and becomes more and more distressing with further increase in myocardial insufficiency. Dyspnea of such severity as to render lying flat in bed difficult or impossible is called *orthopnea*.

Failure of the left ventricle alone gives rise to congestion in the pulmonary vascular circuit with consequent dyspnea, diminution in vital capacity, cough, sputum (sometimes blood tinged) and moist rales (which appear first at the lung bases and later throughout the lungs) it may be accompanied by attacks of *paroxysmal cardiac dyspnea* which may be attended by asthmatic breathing (*cardiac asthma*) or by *acute pulmonary edema* with copious frothy and frequently blood stained expectoration. *Failure of the right ventricle* occasions congestion in the systemic circulation marked by engorgement and visible pulsation in the neck veins with the individual in the upright position, cyanosis, edema of the feet and legs, engorgement of the liver and albuminuria. In primary failure of the right ventricle cyanosis is often out of proportion to the dyspnea because of the interference with hemorespiratory function occasioned by the primary pulmonary lesion and frequently it is emphasized by a polycythemia brought on by prolonged anoxemia.

Edema usually comes on insidiously at first being present only in the evening and in the feet and ankles of the ambulatory individual disappearing during recumbency at night but with further decrease in cardiac efficiency pitting edema gradually increases in extent until the entire body at times including the arms and even the face is water logged. Massive generalized edema is called *anasarca*. In severe congestive failure there is found *ascites* and not uncommonly there occurs accumulation of fluid in the pleural cavities (*hydrothorax*) and rarely in the pericardial sac (*hydropericardium*). Quite often hydrothorax is limited to the right pleural cavity probably because of engorgement or compression of the azygos vein or the fact that the blood from the right lung must be

lifted a greater distance to reach the left auricle than that from the left lung especially when the patient is inclined to lie on the right side (as is frequently the case) or a combination of both these factors.³⁷ Not infrequently pain and tenderness over the liver constitutes a complaint particularly when failure of the right ventricle occurs suddenly and when functional insufficiency of the tricuspid valve exists the liver can be felt to pulsate with each ventricular systole. Nausea and vomiting occasionally occur and in severe cases at times bloody stools may be passed. Jaundice occurs but seldom usually it is a sign of severe failure with a bad prognosis. As pointed out by Meakins³⁸ the skin over the edematous areas is usually not jaundiced while elsewhere striking icterus may be present. In advanced congestive failure the urine is high-colored scanty and of high specific gravity and may contain albumin casts and blood. Urine of low specific gravity is suggestive of a primary contracted kidney secondary to arterial hypertension.

The velocity of blood flow in congestive heart failure is often but not always decreased. Blood pressure measurements of different patients may show variations from marked hypertension to hypotension but in a given individual a rapid or steady drop from a high level to hypotension or normal may be indicative of myocardial insufficiency. The basal metabolic rate is somewhat increased in that dyspnea cough and even the heart itself through its larger bulk and inefficiency entail a greater consumption of oxygen. The vital capacity of the lungs (amount of air that can be expired after the greatest possible inspiration) normally about four to five liters in the male and three to four liters in the female varies inversely with the degree of myocardial inefficiency and in severe failure it may be increased from as low as 0.5 liter or less to the range of normal through improvement in the circulatory efficiency brought about by rest digitalis diuretics and other therapeutic measures.

Roentgenologic examination is of value in congestive heart failure in helping to distinguish the type of lesion present by the cardiac outline to determine the degree of cardiac enlargement particularly in checking change in size as in the acute dilatation which occasionally accompanies acute rheumatic carditis and coronary thrombosis and to demonstrate the extent of pulmonary congestion including the presence or degree of hydrothorax. The electrocardiogram is of value in distinguishing the various types of cardiac arrhythmia in demonstrating

myocardial degeneration, particularly advanced coronary artery disease, through changes in the Q R-S complexes and T waves, and in following the course of digitalis therapy

COMPLICATIONS AND SEQUELAE

Serious complications of congestive heart failure may arise through disturbance of the function of various organs by the circulatory stasis, and occasionally from progression of the disease process causing the myocardial failure. A vicious cycle tends to exist. Impairment of the coronary circulation promotes further myocardial degeneration. Hydrothorax and ascites interfere with expansion of the lungs, and also directly hinder the heart action through displacement, and hydropericardium causes particular cardiac embarrassment by impairing the ability of the heart to fill.

Long continued stasis in the portal circulation may cause cirrhosis of the liver, chronic gastritis with dilatation and ulceration of the stomach, intestinal stasis, splenic enlargement, hemorrhoids, and emaciation, renal insufficiency may give rise to nitrogen retention and occasionally uremia, massive edema of the extremities may result in ulceration and infection with the possibility of streptococcic septicemia which may prove fatal. Thrombosis in the auricles, veins, and occasionally in the arteries at times occurs, and emboli may lodge in the systemic and pulmonary circulation. In advanced failure of long standing, especially in elderly individuals with narrowing of the cerebral arteries, mental apathy, delirium and even coma may be presented. One of the most frequent immediate causes of death in congestive heart failure is bronchopneumonia.

DIFFERENTIAL DIAGNOSIS

The diagnosis of congestive heart failure usually is not difficult, being established by the presence of dyspnea, dependent edema, engorgement of the neck veins and enlargement of the liver, the finding of serious organic changes in the heart, and favorable response to digitalis therapy. However, cases of early myocardial insufficiency without obvious congestion in the systemic vascular circuit, presenting only dyspnea on exertion, fatigue and possibly palpitation or slight precordial discomfort, often require careful study for differentiation from neurocirculatory asthenia, the influence of obesity, and the lack of physical training. Pulmonary symptoms and signs are not due to heart disease unless there

is evidence of the latter in the form of cardiac enlargement, murmurs of valvular deformity, or myocardial infarction. Mistake is less apt to occur in the differentiation of congestive heart failure from nephritis, cirrhosis of the liver, dietary deficiency disease, peritonitis, myxedema, lymph edema, malignancy, pulmonary disease, and constrictive pericarditis if the fact is borne in mind that in congestive heart failure peripheral edema, engorgement of the neck veins, and enlargement of the liver generally occur together and in association with dyspnea. Bilateral engorgement of the veins of the neck without enlargement of the liver suggests the possibility of obstruction of the superior vena cava, but atrophic cirrhosis of the liver may be responsible for the same discrepancy when congestive heart failure is present. Constrictive pericarditis (acute or chronic) often is marked by engorgement of the systemic veins, enlargement of the liver, and dependent edema without a comparable degree of dyspnea, and the heart is usually normal or but little involved, and furthermore the patient usually is young and digitalis therapy effects no benefit.

PROGNOSIS

The prognosis in congestive heart failure is determined by the degree of congestion, the etiological factors, the mode of onset, the age of the patient, and the probable response to treatment. Often it is well to refrain from making a prognosis until the effect of treatment has been observed. Generally speaking, patients who improve on rest alone do well for a period of years; the outlook is less favorable when symptoms and signs disappear rapidly under digitalis therapy but failed to do so with rest only, and when rest and digitalis fail to give relief and diuretic or surgical procedures are necessary to eliminate subcutaneous edema and effusion into serous cavities, the prognosis, regardless of etiology (in the absence of acute inflammation of the myocardium) is grave.

Recognition of the *underlying cause* of the cardiac condition and of the *immediate precipitating factors* is of the utmost importance in predicting the clinical course. Although many of the underlying causes of heart disease do not respond to treatment, many precipitating factors are preventable and controllable. Of the commonest underlying causes, namely, vascular disorders (including hypertension and arteriosclerosis), rheumatic fever, and syphilis, specific therapeutic measures are available only in syphilis. But after syphilitic heart disease is established, specific

treatment is of limited value; although symptoms at times are relieved and the progress of the condition may be retarded, the disease is rarely terminated by therapy. Of the less common underlying causes of heart disease, thyrotoxicosis and pericarditis may be successfully treated by surgery; severe anemia and deficiency diseases usually respond well to therapy; but there is no beneficial treatment for congenital heart defects, bacterial endocarditis, and extensive pulmonary fibrosis.

The average duration of life after the onset of congestive heart failure is in general but a few years. There are great variations, however; and furthermore the cases of many elderly individuals who have dyspnea on exertion for many years but who do not consult a physician are apt not to be included in statistical studies. Each case requires individual consideration. Slight congestive failure due to mitral stenosis or long standing hypertension may be controlled for many years by restriction of activity and digitalis therapy, whereas congestive failure with syphilitic aortitis and aortic regurgitation or with coronary occlusion always bears a more grave prognosis—the degree of failure rapidly increasing and life lasting but a few months to a few years. Paroxysmal cardiac dyspnea, with or without cardiac asthma, always is attended with a serious prognosis. Congestive heart failure which suddenly follows an acute infectious cold usually disappears with the causative factor; but when precipitated by pneumonia or chronic rheumatic infection the prognosis is less favorable. Failure developing in an individual with sedentary occupation usually is more serious than failure of similar degree occurring with heavy manual labor; and when occurring with no temporary or removable cause in a patient already bedridden it is of extremely serious significance. In every case the faithfulness of the patient in following the treatment prescribed is an influential factor in the ultimate outcome.

THERAPY

Aim of Treatment: The treatment of congestive heart failure calls for measures which decrease the work of the heart and increase the efficiency of its action. Such measures include: Rest, the administration of digitalis, diuretics and other drugs, including sedatives, hypnotics, stimulants and cathartics, the regulation of diet, including the restriction of fluid and salt intake, and surgical procedures, such as venesection and paracentesis. In every case it is essential to determine the underlying disease process, and to discover the possible existence of an immediate

precipitating factor, so that available measures can be directed to their prevention and control

Rest. In the treatment of heart failure, rest is imperative. Through rest there results usually a slowing of the rate of the heart with a decrease in the energy expenditure, and opportunity is afforded for the building up of myocardial reserve. Rest of the body and mind is often in itself sufficient to relieve dyspnea, edema, enlargement of the liver and other manifestations of myocardial insufficiency. The amount of rest necessary depends on the degree of failure, it may vary from slight restriction of activities to absolute rest in bed for a period of weeks or months. In failure of slight degree, with dyspnea on moderate exertion only, slight restriction of activity may prove sufficient, but quite often several weeks of complete rest in bed proves of distinct benefit. Rest in bed for at least two or three weeks always is indicated when there is shortness of breath at rest or on very slight exertion.

In severe congestive failure, when moderate or greater pitting edema of the extremities, engorgement of the veins of the neck and hepatic enlargement are present in addition to orthopnea, *absolute rest in bed* is necessary with constant care both day and night. With head elevated in the best position for breathing and relaxation, the patient should not be allowed to reach for any object, to feed or wash himself, read, write or change position without being lifted by an attendant and talking should be discouraged. The bed should be narrow with good spring mattress. A bedstead with back rest and thigh rest such as a Gatch bed, or with an adjustable foot rest resembling an easy chair is most convenient⁸² (Figs. 1 and 2). However, pillows supported by an overturned chair may serve satisfactorily as a back rest, and a wooden support under the mattress can support the knees. A footboard, 36 inches by 16 inches by 1 inch padded with a pillow, will help the patient in retaining his position and lighten the weight of the bedclothing. Tying the pillows in place with loops of one inch gauze bandage assists the patient in maintaining his position and small pillows beneath the arms and under the head promote comfort and relaxation. In cases with severe orthopnea a cardiac table (padded by a feather pillow), extending across the bed provides a change of position serving as a head and arm rest. The room should be quiet and pleasant with cheerful decorations and the maximum of sunshine, the temperature should not be over 20° C (68° F), with

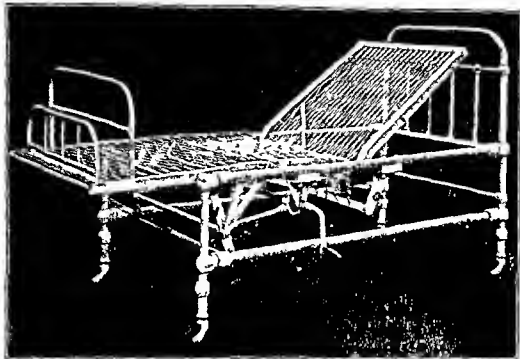


FIGURE 1 The cardiac bedstead (Lewis) with back rest in position

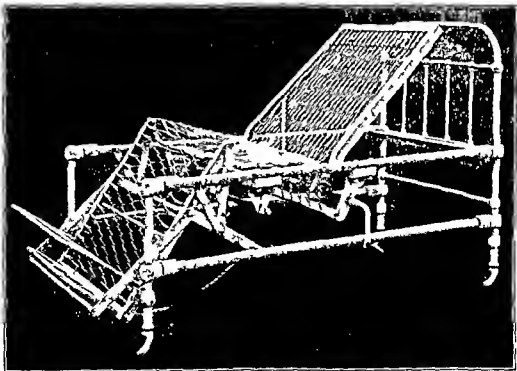


FIGURE 2 The cardiac bedstead (Lewis) with back rest, thigh rest and lowered leg rest—converting the bed into a chair

seeds of digitalis are used in the manufacture of the so-called digitalins of commerce the chief ones of which are true digitalin (*Digitalinum verum*) and digitalein

Most of the preparations of digitalis on the market are properly standardized and reliable. Preparations of the powdered whole leaves in the form of compressed tablets, pills or capsules are just as effective as the tincture and because of the ease in handling exactness of dosage and stability are more generally acceptable. Powdered leaf preparations if kept dry retain their effectiveness for many years. Although the one hour frog method is still recommended in the U. S. Pharmacopoeia for the standardization of preparations of digitalis, *strophanthus* and squill during recent years the intravenous cat method of Hatcher and Brody⁶⁰ has become quite widely used. A cat unit is the minimum amount of digitalis which is required per kilogram (2.2 pounds) of body weight to kill a cat when injected slowly and continuously by vein—in about 90 minutes it represents 100 mg (1 1/2 grains) of powdered leaves or 1.0 cc (15 minims) of tincture of digitalis or 1/10 mg (1/650 grain) of ouabain. Theoretically, one cat unit is the equivalent of 167 frog units.

The isolated digitalis principles are being used more and more extensively in clinical practice. In a six year clinical study of ambulatory patients with established auricular fibrillation at the Pennsylvania Hospital it has been found that 0.1 Gm (1 1/2 grains) of digalen, 1/4 mg (1/40 grain) of verodigen (the gitalin glucoside of *Digitalis purpurea*), 1/4 mg (1/40 grain) of digoxin (from the leaves of *Digitalis linata*) and 1/10 mg (1/650 grain) of Digitaline Cristallisee Nativelle are respectively equivalent to one cat unit or 0.1 Gm (1 1/2 grains) of standardized digitalis leaves and that none of the preparations proves more efficacious than any other. Because of the difference in strength and the danger of confusing them use of the digitalins (French, German and true) is not to be recommended.

Therapeutic Action of Digitalis The beneficial effects of digitalis in heart failure arise from (1) its action on the cardioinhibitory mechanism and (2) its direct action on the myocardium. The cardioinhibitory effect results from (a) stimulation of the vagus center in the medulla and (b) direct action on the sinoauricular node, the auricular and ventricular muscle and the conduction pathway between the auricles and the ventricles.

With the exception of cases with vagal activity more sensitive than the average (such as is commonly present in young individuals) slowing of the heart with regular rhythm generally is possible only by giving an amount of digitalis capable of producing toxic symptoms. In elderly individuals and during fever therapeutic doses are particularly apt not to effect slowing because of the existence of an abnormal relative diminution of vagal tone. However excessive doses of digitalis can cause inhibition of the generation of cardiac impulses with consequent marked sinoauricular bradycardia sinus arrhythmia and even auricular standstill.

The ability of digitalis to increase the tone of the myocardium and the force of systole has been for many years an accepted fact and only during recent years has it become established that the effect of digitalis on the output of the normal heart is different from that in the case of the dilated heart of myocardial failure. In an experimental study on dogs Harrison and Leonard¹⁶ (1956) demonstrated that the calculated

full therapeutic dose of digitalis caused an average decrease of approximately 25 per cent in the cardiac output per minute and Burwell, Neighbors and Regen¹⁷ found a similar diminution of cardiac output in normal men following the administration of from 1.4 to 2.7 Gm. (22 to 42 grains) of digitalis leaves. From studies of the cardiac output of normal men, patients with congestive heart failure and dogs with and without enlarged hearts, Cohn and his associates^{18, 19, 20, 21} have concluded that digitalization causes a tendency toward a decrease in cardiac output through an increase in cardiac tone and a simultaneous tendency toward an increase in cardiac output through an increase in the extent of ventricular contraction and that the cardiac output at any instant is the net result of these opposing factors. In heart failure the length of the cardiac muscle fibers has been increased beyond a certain optimal length with a resultant decrease in the cardiac output (described by Starling^{19, 20} as the law of the heart) and under the influence of digitalis it is believed that dilatation of the heart chambers beyond the physiologic limit may be relieved through an increase in the tone. The optimum cardiac output is rendered possible through a simultaneous increase in the extent of ventricular contraction. In other words the change in cardiac output which results from the action of digitalis depends upon the initial size of the heart (ventricular chambers); there is a decrease

in the output of normal hearts and an increase in the output of dilated hearts

The bulk of evidence is against therapeutic doses of digitalis having any direct effect on the blood vessels of man. The change in blood pressure which occurs with digitalization is a mere readjustment, the result of general improvement in the circulation. Also it is quite generally agreed that the diuresis produced by digitalis in congestive heart failure is entirely secondary to improvement in the circulation, particularly the circulation of the kidneys. Only in the presence of congestive heart failure is digitalis capable of producing diuresis.

Toxic Effects of Digitalis Overdosage of digitalis occasions disagreeable toxic symptoms, and dosage greatly in excess of the estimated therapeutic dose may cause death. Nausea and vomiting—frequently preceded by a day or two of complete anorexia, headache and vertigo—are among the earliest and commonest toxic symptoms. The emetic action of digitalis does not result from direct irritation of the gastric mucosa, but is a reflex phenomenon arising from the direct action of the drug on the heart, the impulses passing from the heart to the vomiting center in the medulla.^{61, 62} In the average ambulatory cardiac patient with moderate congestive failure quite a wide margin generally exists between the minimum dose necessary for the obtaining of full therapeutic benefit and the maximum dose which can be tolerated without symptoms of toxicity, whereas in patients with signs of congestive failure at rest this margin may be so narrow as to render it difficult to avoid precipitating toxic effects.⁶⁰ In severe myocardial failure, vomiting caused by splenic congestion must be distinguished from that which might result from overdosage of digitalis. Vomiting which occurs within a few minutes after a dose of digitalis *very likely has not been caused by the drug*, and may be obviated by administering digitalis in therapeutic doses intravenously or intramuscularly. In rare instances psychic vomiting—occasioned by the bitter taste of the drug—may follow the administration of but one or several doses. When nausea and vomiting are the result of digitalis overdosage, it is better to stop the drug entirely for from one to several days than merely to diminish the dosage, because of the smaller likelihood of causing a future distaste for the drug.

Toxic effects of digitalis on the heart may occur in the form of premature contractions, coupled rhythm, various grades of auriculoventricu-

lar heart block sinus arrhythmia, sinoauricular block, auriculoventricular nodal rhythm auricular standstill intraventricular block, pulsus alternans paroxysmal tachycardia or auricular fibrillation. Most commonly observed are premature contractions and various grades of auriculoventricular heart block the former resulting from increased irritability of the myocardium and the latter from depression of conduction between the auricles and the ventricles. Coupled rhythm (pulsus bigeminus) results from a ventricular premature contraction with compensatory pause occurring immediately after each normal beat. As a general rule reduction of the ventricular rate to 50 or less per minute calls for decrease in dosage or discontinuation of the drug for several days. The toxic significance of acceleration of the rate and the onset of auricular fibrillation must be borne in mind in order to avoid grave results such as ventricular tachycardia or fibrillation or even irreversible cardiac damage, through continuation of the drug.

Other occasional toxic effects are blurring of vision and pronounced disturbances of color vision—objects appearing green yellow white or lavender^{124 138 145} diarrhea¹⁴⁵ reduction of the output of urine and acute psychopathic outbreaks¹³⁸

The maximum therapeutic benefit from digitalis has been estimated to result from the administration of approximately 20 to 40 per cent of the lethal dose¹¹², yet despite the fairly wide margin of safety fatalities occasionally do attend its administration. Death usually is preceded by ventricular fibrillation which is especially liable to be induced in patients with impaired intraventricular conduction. Differences in individual susceptibility to the drug and in the margin of safety in the various degrees of failure at times may be responsible for severe poisoning. And the possibility of danger resulting from the combined effect of digitalis with other drugs demands consideration. Cases of death within a few minutes immediately following the intravenous injection of 10 cc of a 10 per cent solution of calcium chloride and of calcium gluconate respectively, in patients who had been receiving digitalis beforehand have been reported^{11 42 84 85}. Quinidine in doses which are never fatal in the normal undigitalized animal may cause death in the presence of toxic rhythms induced by digitalis^{51, 79}. And about one half the medial lethal dose of ephedrine hydrochloride has been found to prove fatal in an

mals in the presence of about one half the medial lethal dose of digitalis or ouabain 70

Indications for Digitalis Therapy The most striking benefit of digitalis therapy is observed in congestive heart failure with auricular fibrillation or auricular flutter with rapid ventricular action. In such cases the improvement in circulatory efficiency results not only from the direct action of the drug on the myocardium but also in large part from its action on the cardioinhibitory mechanism: the ventricles through increase in the refractory period of the auricular and the ventricular muscle and the depression of conduction between the auricles and the ventricles are afforded rest from the abnormally large number of impulses from the auricles. However in congestive failure with regular sinus rhythm digitalis also proves of great value—solely through increase in the efficiency of ventricular systole in fact at times it is life saving.

Digitalis does not have the ability to abolish auricular fibrillation which has been present for any length of time. Occasionally so great a diminution in the irregularity of ventricular action accompanies slowing of the rate that regular rhythm is apparently restored but the fallacy of such belief is readily shown by electrocardiographic examination. If normal sinus rhythm is resumed during the administration of digitalis the change occurs in spite of the drug the total arrhythmia having been merely of the paroxysmal type.

The state of optimum digitalization is determined through close observation of each patient. The optimum ventricular rate at rest is usually between 70 and 80 beats per minute but occasionally some individuals do better with a rate as low as 50 to 60 per minute and others such as cases of aortic insufficiency often feel at their best with a rate of about 90 per minute. The heart rate should be determined at the apex because of the not infrequent presence of a pulse deficit (difference between the ventricular rate at the apex and the pulse rate at the wrist) which tends to disappear under digitalis therapy.

The presence of a moderate number of premature contractions (extrasystoles) in congestive failure is not a contraindication to the use of digitalis in fact at times premature contractions disappear under digitalization. However when ectopic beats are so numerous that the state of congestive failure might possibly be a result of the arrhythmia caution should be exercised in the administration of the drug because of the

danger of precipitating paroxysmal ventricular tachycardia or ventricular fibrillation with possible fatal termination. The inception of bigeminal rhythm or of runs of premature contractions during digitalization is a danger signal demanding discontinuation of the drug. When partial auriculoventricular heart block (with mere prolongation of the P-R interval of the electrocardiogram or occasional dropped beats) is shown on electrocardiographic examination the danger of causing complete auriculoventricular dissociation with further impairment of circulatory efficiency must be borne in mind. But in complete heart block of permanent type with manifestations of congestive failure digitalis may occasion benefit through increase of systolic efficiency.

Not uncommonly an elevated systolic blood pressure falls and an abnormally low systolic pressure due to myocardial insufficiency is brought nearer to the normal level by digitalis therapy. Particularly striking is the tendency to lower the elevated diastolic pressure and to increase the diminished pulse pressure so frequently present in congestive failure. Patients with actual nephritis as a complication of myocardial failure tolerate digitalis well. Relief is not infrequently effected by digitalis in paroxysmal cardiac dyspnea (cardiac asthma) even when signs of failure are limited to the pulmonary circuit. In angina of effort without evidence of congestive failure digitalis seldom proves of value. But not uncommonly, probably by aiding in the improvement of myocardial efficiency it does relieve the more continuous types of precordial or angular pain which at times occur in congestive failure. In coronary thrombosis accompanied by signs of congestive heart failure digitalis is indicated particularly if auricular fibrillation with a rapid ventricular rate is present. In severe failure it may prove a life saving measure.

In the treatment of congestive failure due to active enditis caused by rheumatic fever the benefit resulting from digitalis therapy quite often is less striking than in myocardial insufficiency which has developed gradually over a period of years and in which congestive failure is precipitated by respiratory infection, overexertion or some other factor. In the administration of digitalis to children slowing of the heart with regular sinus rhythm usually is not pronounced and the incidence of toxic effects is not infrequent. The possibility of auricular fibrillation as a toxic manifestation of the drug must not be overlooked. 74 116 Elec

trocardiograms should be taken at intervals in order to detect partial auriculoventricular heart block or any other disorder of rhythm.

The use of digitalis is not indicated in the treatment of acute peripheral vascular failure (shock, collapse), with rapid, thready pulse and low blood pressure—in the absence of myocardial failure. In this condition therapeutic measures should be directed to the vasomotor system and the restoration of blood volume rather than to the heart.

Administration of Digitalis. In prescribing digitalis it is essential to bear in mind that a certain amount of the drug must be accumulated in the body before therapeutic effect will become manifest; that when administered over a period of time at a rate faster than that of elimination and destruction, the action of digitalis becomes more and more pronounced (*cumulative action*), and that its effect, once apparent, is very prolonged, and can be maintained by dosage equivalent to the amount destroyed or eliminated from the body each day. The effect of digitalis on the heart muscle fibers, as shown by changes in the T wave of the electrocardiogram, begins between two and four hours after the administration by mouth of a dose of 0.065 Gm. (1 grain) of powdered leaves per ten pounds of body weight (or 0.06 cc. or 1 minim or more of a standardized tincture, a ten per cent solution, for each pound of body weight), reaching its maximum in from the sixth to the twenty-fourth hour,^{13, 104, 129, 159} which may then persist as long as 4 to 15 days after discontinuing its use.^{129, 159} *In view of the persistence of action, there should be certainty before prescribing large doses of digitalis that no digitalis body in therapeutic amount has been taken during the preceding ten days or two weeks.*

The principle of digitalis dosage proposed by Withering¹⁴⁵ (1785), namely, "Let it be continued until it acts either on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects," still holds good with the exception that effort always should be made to avoid distressing gastric toxic effects. Although it is possible that small so-called tonic doses of 0.03 to 0.1 Gm. (½ to 1½ grains) of whole leaf (equivalent to 0.3 to 1 cc. or 5 to 15 minims, not drops, of the tincture) may help individuals with poor cardiac tone, doses of such size are *not* effective in cases with signs of advanced congestive heart failure. In general, the dosage of digitalis varies directly with the body weight. Feggleston³⁶ (1915) found the

average dose necessary to produce "full therapeutic" or "minor toxic" effects to be 0.146 cat unit per pound of body weight—that is, about 22 cat units or 2.2 Gm. (33 grains) of whole leaf (corresponding to 22 cc. or 330 minims of properly standardized tincture) for an individual weighing 68 kilograms (150 pounds). This figure represents the amount of digitalis which may be expected to produce the highest possible degree of effect in the therapeutic zone. And it is known that in the average patient with failure of mild or moderate degree there exists a wide margin between the minimum dosage necessary for optimum therapeutic effect and the maximum amount that can be tolerated without toxic effects.⁵⁰

On the basis of body weight alone it is not possible to calculate accurately the total dosage which will be required to secure full therapeutic effect in a given case. Extremely thin or elderly individuals tend to require a smaller amount than do light adults; children of four years of age or older, weighing over 40 pounds, require about 50 per cent more digitalis per unit of body weight than is needed by adults, while younger children, between 16 and 40 pounds in weight as a rule respond to digitalis more readily than do adults.⁹³ Also, the presence of an abnormal vagus accelerator balance with marked acceleration of the rate, such as is likely to accompany fever, hyperthyroidism, neurocirculatory asthenia, and childhood, tends to require a relatively greater amount of digitalis, with a resultant narrowing of the margin of safety between the stage of therapeutic benefit and that of toxic effects.¹⁰ As a rule, the more advanced the degree of failure, the greater is the total dosage necessary for the securing of full therapeutic benefit within a given period of time. In addition, it is not always possible to weigh the patient and to estimate correctly the amount of edema. *Clinical experience shows that each case must be studied individually*—with consideration of the influence which body weight bears on the total dosage.

For adults of average size, between 57 and 80 kg. (125 to 175 pounds) in weight, the amount of digitalis needed to secure full therapeutic effect varies from 1.3 to 1.6 Gm. (20 to 24 grains) of whole leaf (equivalent to 13 to 16 cc. of the tincture) in about 90 per cent of cases when administered in a period of 24 hours; and the remaining individuals require a larger quantity, which in some instances amounts to 2 Gm. (30 grains) or more of whole leaf (which corresponds to 20 cc. or more

of the tincture) In congestive failure of severe degree with the patient confined to bed it is generally quite safe to administer in divided doses 1 cc Gm (18 grains) of whole leaf (or 1 cc of the tincture) within a period of 24 hours Provided no digitalis body in therapeutic amount has been taken by the patient during the two weeks immediately before hand such dosage will not occasion toxic symptoms except in the possible rare case of unusual susceptibility to the drug Four tenths of a gram (6 grains) of the whole leaf—in the form of four tablets or enteric coated pills of 0.1 Gm or 1½ grains or one cat unit each—can be given every six hours for three doses (equivalent to 4 cc or 60 minims or 12 drops of the tincture every six hours for three doses) and if no digitalis effect is evident at the end of 24 hours the drug is continued in doses of 0.1 or 0.2 Gm (one or two pills of 1½ grains each or 1 or 2 cc—15 or 30 minims—of the tincture) every four or six hours—depending on the urgency of the condition the size and the age of the patient—until the desired result is obtained The appearance of signs of clinical improvement namely slowing of the heart rate taken at the apex relief of dyspnea diuresis and the disappearance of cyanosis edema and venous congestion is an indication that the patient's system has become saturated with the drug and that the daily dosage should be reduced to the minimum amount necessary for the maintenance of digitalization

In failure of mild or even of moderate degree such as is frequently presented by ambulatory patients rapid digitalization is not necessary Full therapeutic effect usually can be secured in a week by the administration of one 0.1 Gm (1½ grain) pill three times each day after meals (equivalent to 1 cc or 15 minims of the tincture three times a day for one week) Somewhat smaller daily amounts will accomplish full digitalization in a period of time somewhat longer than a week Because of the fact that a percentage of the drug in the body is excreted or destroyed each day a larger total amount of digitalis is needed when digitalization is brought about over a period of days

After the full therapeutic effect of digitalis has been established it is maintained by the daily administration of a dose corresponding to the amount of the drug, excreted or destroyed each day The amount of digitalis effect which disappears from the body after full digitalization has been calculated to average 1 cc cat units or 15 cat units every 24 hours in studies based upon the appearance of minor toxic symptoms¹⁰⁷ or

changes in the T wave of the electrocardiogram¹³ There is a distinct variation in the quantity eliminated each day by different individuals and more recent studies have shown the rate of elimination to vary directly with the concentration of the drug in the body^{48 49 100} Clinical experience has shown that a daily dose of 0.1 Gm ($1\frac{1}{2}$ grains or 1 cat unit) tablet of the whole leaf (equivalent to 1 cc or 15 minims not drops of the tincture) very frequently proves adequate for the maintenance of full therapeutic effect in the average adult patient Therefore it is well to try such an amount for a period and then if found unsatisfactory it can be increased or decreased later Each case must be studied individually the exact amount necessary being dependent on the particular individual's body weight susceptibility to digitalis degree of myocardial failure and physical activities The daily requirement for children or very slender frail adults may be as small as 0.05 Gm ($\frac{3}{4}$ grain or $\frac{1}{2}$ cat unit) while in others as much as 0.2 or 0.3 Gm (two or three $1\frac{1}{2}$ grain pills) may be necessary to prevent the recurrence of manifestations of failure and further crippling Not infrequently patients learn quite well how to regulate their own daily requirement

After the optimum daily dosage has been determined and the patient has adapted himself to the limitations of his physical activities the same dosage may be used regularly for months or years with but little or no change Practically always after severe failure the need for digitalis continues for the remainder of life And through its constant use life and also the ability to carry on gainful occupation can be prolonged for years Except for the diminution in effectiveness resulting from progressive degenerative changes in the myocardium incident to advancing years digitalis does not lose its efficacy when continued over a long period of time

To follow the effect of digitalis in congestive failure it is well to keep a careful chart of (1) the dosage (2) the heart rate at the apex and the pulse deficit (difference between the apex and radial pulse rates) particularly if auricular fibrillation is present (3) the fluid intake urine output and loss of weight to follow diuretic action (4) subjective symptoms and signs and (5) the record of any procedure such as the administration of a specific diuretic or the performance of a paracentesis Determination of the vital capacity of the lungs also is of some value in following the patient's condition And the electrocardiogram is of importance at times in determining through changes in the T wave the extent

of digitalis effect. Digitalization usually causes a decrease in the amplitude of the T wave, leading to flattening and in extreme cases deep inversion (following a depression of the S-T interval) in Leads I, II, and III^{13, 24} and similar changes in Lead IV_F (or IV_R).

Administration by Routes Other than by Mouth: When immediate digitalis effect is imperative because of the individual's grave condition, the drug can be given *intravenously* in the same dosage that is used by mouth. If the patient has not taken any digitalis during the two weeks immediately beforehand, 12 cc. of a solution (specially prepared for hypodermic use in sterile ampules or vials), equivalent to 0.6 Gm. of whole leaf may be given at once, slowly, allowing 30 to 45 seconds to complete the injection; and a second dose of 8 cc., equivalent to 0.4 Gm. of whole leaf, may be given in three or four hours. Quite often several hours after the second dose there is sufficient clinical improvement to permit oral administration of a third dose of 0.2 Gm. (3 grains), and a dose of 0.1 to 0.2 Gm. (1½ to 3 grains) six or eight hours later if necessary. Usually the next day a maintenance dosage of 0.1 to 0.2 Gm. (1½ to 3 grains) can be begun. The maximum effect of potent dosage intravenously occurs in about two hours, and lasts one or two days. If intravenous administration is necessary in the case of an individual who recently has been taking digitalis, a dose of 0.2 Gm. (3 grains) may be given, and be repeated at two-hour intervals until a therapeutic or toxic effect becomes evident.

If the urgency of the condition continues, or if administration by mouth is rendered impossible by vomiting, coma or the inability to swallow, the daily maintenance dose may be administered intravenously for an indefinite period. Although for long-continued use intramuscular administration usually is more suitable, the injection may at times cause local irritation or even necrosis. Only when it is impossible to inject the drug into a vein should the intramuscular or subcutaneous method of administration be selected for emergency treatment. Rectal administration of digitalis, either as a slow instillation of the tincture diluted in 60 to 90 cc. (2 to 3 fluidounces) of normal saline solution or as a suppository (after a cleansing enema), is effective in the same dosage as by mouth, intravenously or intramuscularly, but it is apt to be irritating and is unnecessary.

Other Drugs of "Digitalis Series": Of the other members of the "digitalis series," there is no preparation—with the exception of strophan-

thin for intravenous use in rare emergencies—that is superior to digitalis and therefore unless there exists an idiosyncrasy to digitalis or it is impossible to obtain digitalis or strophanthin their use is not to be recommended. Preparations of apocynum⁸⁹ convallaria⁸⁹ strophanthus^{58 59} and of squill itself have been found to be distinctly inferior to digitalis in effectiveness and reliability.

The field of strophanthus therapy is limited to intravenous administration of the strophanthins. Ouabain (gastrophanthin of Thoms) derived from the seeds of *Strophanthus gratus* is a crystalline glucoside which is at least twice as strong as the pharmacopoeial strophanthin (amorphous strophanthin) a glucoside or a mixture of glucosides from *Strophanthus kombé*. Oral administration of preparations of strophanthus is not advocated because of the danger arising from the uncertainty of their absorption from the gastrointestinal tract.

In the treatment of overwhelming failure ouabain (crystalline strophanthin) or the pharmacopoeial amorphous strophanthin may be used intravenously instead of digitalis. It must be borne in mind that ouabain is at least twice as strong as the pharmacopoeial strophanthin that $\frac{1}{10}$ mg ($\frac{1}{100}$ grain) of ouabain is the equivalent of one cat unit. The speed of action of strophanthin when given intravenously is usually more rapid than that of digitalis; an effect becomes appreciable in 5 to 15 minutes; attains its maximum in from 15 to 50 minutes and is maintained for 12 to 24 hours.¹⁵⁰ Large dosage is dangerous and there must be certainty as to whether the individual recently has been taking digitalis. If no digitalis body has been used during the 48 hours immediately preceding a dose of $\frac{1}{10}$ mg ($\frac{1}{100}$ grain) of ouabain may be given intravenously and followed by doses of $\frac{1}{10}$ mg ($\frac{1}{50}$ grain) every half hour until therapeutic or toxic effects become evident and then a dose of $\frac{1}{8}$ to $\frac{1}{6}$ mg ($\frac{1}{400}$ to $\frac{1}{200}$ grain) may be given once every day or two if necessary.

Urginin a mixture of two of the active water insoluble glucosides of squill (crystalline scillonin A and amorphous scillonin B) exerts a beneficial action on the heart in congestive heart failure with or without auricular fibrillation.^{19 20 87} It is available in tablets of $\frac{1}{6}$ mg ($\frac{1}{120}$ grain) each for administration by mouth; two tablets are equivalent to one 0.1 Gm ($\frac{1}{10}$ grain or one cat unit) tablet, capsule or pill of whole leaf of digitalis. Urginin offers no advantages over digitalis.

in the treatment of myocardial insufficiency only in the unusual instances in which nausea or vomiting due to an idiosyncrasy or prejudice renders it impossible for the patient to take the amount of digitalis necessary for full therapeutic effect should ougmin be substituted for digitalis. No primary diuretic action of squill has ever been demonstrated.

Thevetin, a cardiac glucoside from the nuts of the tropical bell tree *Thevetia nereifolia* (Jussieu) related to *apocynum* is one eighth to one seventh as potent as ouabain.²¹ When administered intravenously it has been found capable of restoring and maintaining circulatory efficiency in some cases of congestive failure but its inherent tendency to produce untoward gastrointestinal effects particularly cramps and diarrhea renders oral administration unfavorable.^{3, 32, 37} At present its use is not to be recommended.

Changing from one preparation of digitalis to another with the hope of obtaining better results is as a rule quite unnecessary since therapeutic effects can be achieved with any active preparation if administered in sufficient dosage. An exception is the very rare case with a hypersensitive reaction to digitalis for whom a preparation of some other drug of the digitalis series may prove tolerable without toxic effects whereas digitalis in dosage less than the amount required for therapeutic effect occasions nausea and vomiting. As a general rule however the toxic and therapeutic effects of preparations of digitalis or of any other drug of the digitalis series are parallel; a preparation that can be taken in very large dosage without toxic symptoms is likely to be inactive therapeutically and one that is very active therapeutically tends quickly to produce toxic effects. There is no proof that the higher priced preparations possess any greater therapeutic efficacy than those of lower price.

Other Cardiac Drugs. *Epinephrine* (adrenalin) has no specific value in the treatment of congestive heart failure; its chief value lies in the revival of heart action in the ventricular standstill of the Adams-Stokes syndrome or in severe sinoatrial depression when it is administered subcutaneously or intravenously in doses of 0.25 to 1 cc. of the 1:1000 solution (equalling 0.25 to 1.0 mg.) of the hydrochloride at intervals of every few hours as needed.¹⁴⁸ At times it proves helpful secondarily in paroxysmal cardiac dyspnea with severe bronchial spasm but its use in such cases must be attended with caution. *Ephedrine* resembles epinephrine in action although its effect is less intense and more prolonged --

The usual clinical dosage of ephedrine hydrochloride is 25 to 50 mg ($\frac{3}{8}$ to $\frac{3}{4}$ grain) by mouth three to six times daily. It is less likely to produce dangerous ventricular tachycardia or ventricular fibrillation than is a large dose of epinephrine. Occasionally, however, nervousness results from its use.

Caffeine, although of some value as a circulatory and respiratory stimulant, is not a substitute for digitalis in congestive heart failure. The xanthine (purine) compounds, namely, caffeine, theobromine, and theophylline, are quite generally believed to have a dilating effect on the coronary vessels with a resultant increase of blood flow through the myocardium,^{31, 43, 110-121} although some investigators have not been able to demonstrate their efficacy. Nevertheless, some patients with cardiac pain do respond favorably to the xanthines, particularly to theophylline sodium acetate, 0.25 Gm (4 grains), theobromine sodium acetate, 0.5 Gm ($7\frac{1}{2}$ grains), theophylline calcium salicylate (phylicin), 0.5 Gm ($7\frac{1}{2}$ grains), and theophylline ethylenediamine, 0.2 Gm (3 grains).¹⁴ Caffeine citrate has little or no therapeutic value as a coronary artery dilator. Caffeine sodium benzoate in dosage of 0.3 to 1.0 Gm (5 to 15 grains) subcutaneously or intravenously, as also theophylline ethylenediamine in dosage of 0.25 to 0.5 Gm ($3\frac{3}{4}$ to $7\frac{1}{2}$ grains) diluted to 10 cc. administered slowly intravenously is of value in the relief of Cheyne-Stokes respiration. Theophylline ethylenediamine administered intravenously, through its ability to relieve bronchial spasm,⁶⁶ proves of particular benefit in paroxysmal cardiac dyspnea (cardiac asthma). The xanthine derivatives also have primary diuretic action.

Camphor and its allies have but little, if any, effect on the action of the heart.⁸⁸ In experiments on animals camphor dilates the coronary vessels but it is not certain that this occurs in man with therapeutic doses.³¹ Improvement in the pulse which at times is observed after subcutaneous injections of camphor in dosage of 0.2 Gm (3 grains) in oil may be due to the local irritation causing a reflex rise of blood pressure and stimulation of respiration. Cardiazol, also known as metrizol, is a synthetic compound (pentamethylenetetrazol), which has been recommended for circulatory failure as an improved substitute for camphor; it does stimulate the respiratory and vasomotor center, but its value as a cardiac stimulant is somewhat questionable.¹⁵ Coramine, chemically pyridine β carboxylic acid diethylamide, also has been widely used as a

respiratory and circulatory stimulant, especially in cases of overdosage with morphine, avertin or other narcotics¹⁴⁹ Its effect on the human respiratory center depressed by morphine is less rapid and prolonged than that of cardiazol It does cause an elevation of blood pressure through stimulation of the vasomotor center, but whether it stimulates the heart directly has not been established In dosage of 2 to 4 cc. intravenously it is of value in the relief of Cheyne Stokes respiration and paroxysmal cardiac dyspnea

Strychnine does not stimulate the heart directly,¹²⁷ although it may produce mild vasoconstriction through action on the medullary center Sparteine, an alkaloid found in the common broom plant and in various species of lupines, has been exploited for use in heart disease largely because of its supposed value as a diuretic, but it has proved of no value Cactus also is of no benefit as a cardiac remedy Mention should be made of the fact that the use of quinidine generally is forbidden in patients with marked cardiac enlargement, or with history or signs of congestive heart failure

Oxygen Inhalation of 40 to 50 per cent oxygen by means of a special tent, chamber, hood, mask, or double nasal catheter or oropharyngeal catheter holds an important place in overcoming marked dyspnea and cyanosis in acute congestive heart failure, and in the treatment of serious complications such as pulmonary infarction and pneumonia⁵ Administration by catheter is the least satisfactory, and should be employed only if no other appliance is available In arteriosclerosis or coronary heart disease of long standing with severe manifestations of failure not relieved by rest, digitalis or other therapy, oxygen inhalation brings about slowing of the heart rate, and relief of dyspnea, cyanosis, restlessness, and Cheyne Stokes respiration, if present, and residence in an oxygen tent or chamber over a period of days or even weeks occasionally promotes diuresis, with possible subsequent restoration of myocardial efficiency Oxygen treatment before and after operation is valuable in preventing postoperative complications in advanced myocardial insufficiency, particularly in cases of hyperthyroidism In acute pulmonary edema due to sudden failure of the left ventricle positive pressure of helium oxygen to compensate for the increase in internal capillary blood pressure is of special benefit⁶ In acute coronary thrombosis with evidence of severe anoxemia, inhalation of oxygen not uncommonly proves a life saving measure, oxygen

concentration as high as 90 to 100 per cent for the first 12 hours is of critical value.

Intravenous Glucose: Intravenous administration of a hypertonic glucose solution is at times helpful in obstinate cases of congestive heart failure, in relieving paroxysmal cardiac dyspnea, and in the treatment of shock following coronary thrombosis. From 50 to 100 cc. of a 50 per cent solution (or 200 to 250 cc. of a 10 to 20 per cent solution), warmed to body temperature, are injected slowly once or twice daily for several days. Its value is ascribed to the nutrient effect on the myocardium and the diuretic action of glucose. The administration of blood serum intravenously in conjunction with glucose solution may prove of benefit in obstinate cases of congestive failure with a definite depletion of blood serum protein.

Diuretics: The use of drugs with primary diuretic properties such as the xanthine (purine) derivatives, mercury, bismuth and certain salts is indicated in congestive heart failure when edema and dyspnea persist after rest, digitalis in adequate dosage, and restriction of fluid and salt intake. Through diuresis the heart is relieved of the added burden of propelling the blood through the compressed blood vessels, the blood volume is decreased,³⁷ and in all probability the efficiency of the heart is increased by loss of edema from the myocardium. Ascites due to congestive heart failure generally disappears under diuretic therapy. But hydrothorax, on the other hand, tends to remain unchanged, and should be removed by mechanical means in the beginning of the treatment. Not infrequently abdominal paracentesis, and at times thoracentesis, results in a marked improvement in urinary excretion. In cases with little or no peripheral edema but with dyspnea and other manifestations of pulmonary vascular congestion in spite of full digitalization, relief occasionally is afforded by use of a xanthine or a mercurial diuretic.^{1, 44, 81} In the selection of a diuretic for use in a given case, factors demanding consideration are: The presence of nausea or vomiting, the existence of nephritis, and the necessity for prompt diuresis.

XANTHINE PURINE GROUP: Generally speaking, in the absence of nausea, vomiting and urgent emergency, it is well to administer a xanthine preparation by mouth before resorting to the new mercurial compounds which must be given intravenously or intramuscularly, or in the form of rectal suppositories. Of the xanthines, theophylline (or theocin)

possesses greater diuretic effect than theobromine and the latter is stronger than caffeine but the degree of gastric irritation occasioned by each is in reverse order 31 63 All xanthine preparations should be administered intermittently with a free interval of several days after several days of administration otherwise in initial diuresis will fall quickly to the previous level In about one half of the cases with edema persisting after rest and proper digitalization theobromine or one of its salts produces satisfactory diuresis Theobromine sodium salicylate (diuretin) U S P in doses of 0.5 to 1.0 Gm ($7\frac{1}{2}$ to 15 grains) by mouth three or four times a day for several days and repeated at intervals of several days often proves effective as also does theobromine sodium acetate administered in similar dosage Theobromine calcium salicylate (theocalcin) in doses of 1.0 to 1.5 Gm (15 to $21\frac{1}{2}$ grains) three or four times a day is said to be more effective and more easily tolerated than diuretin and theocin 125 Theophylline (theocin) in doses of 0.2 to 0.3 Gm (3 to 5 grains) by mouth three or four times daily after meals for one to three days generally produces diuresis although nausea and more rarely renal irritation or mental aberration may result Although derivatives of theophylline with supposedly less toxic effects are available they almost invariably prove less efficient as diuretics Theophylline ethylenediamine (euphyllin metaphyllin aminophyllin or thephyldine) in doses of 0.09 to 0.18 Gm (1½ to 3 grains) by mouth four times a day occasionally has a satisfactory effect The dosage of theophylline calcium salicylate (phyllicin) is 0.25 Gm (4 grains) and that of theophylline sodium acetate 0.2 Gm (3 grains) two to four times a day by mouth In addition to their usefulness as diuretics the xanthine compounds may prove of benefit by virtue of an active dilating effect on the coronary vessels Also they are of value in the relief of Cheyne Stokes respiration (as mentioned in discussion of Other Cardiac Drugs)

MERCURY For many years calomel (mild mercurous chloride) has been used as a diuretic being administered by mouth in dosage of 0.06 to 0.12 Gm (1 or 2 grains) two or three times a day for two or three days but care is necessary to avoid disagreeable toxic effects such as stomatitis and diarrhea But since the introduction of merbaphen or novasurol (a mercury urea compound) in 1920 114 mersalyl or salyrgan (a mercury salicylate compound) in 1924 17 and novumit or mercupurin (a mercury theophylline compound) in 1928 72 each prepared in ampules

for use intravenously or intramuscularly, calomel is rarely prescribed for diuretic effect. Salyrgan and the mercury portion of mercupurin (mercurin) are available also in the form of rectal suppositories.

The new mercurial compounds are more rapid in action and more powerful than the xanthine derivatives. And salyrgan and mercupurin are relatively nontoxic. Continued use of novasurol is liable to cause stomatitis, colitis and hematuria, but renal irritation is rarely observed with salyrgan³³⁶ or mercupurin.³⁴ One cubic centimeter of ten per cent solution of salyrgan contains 0.0396 Gm. of mercury, and 1 cc. of 19.5 per cent solution of mercupurin contains 0.0393 Gm. of mercury. Some clinicians have observed a greater diuresis resulting from mercupurin than from salyrgan or novasurol, attributing the difference to the componental five per cent of theophyllin in mercupurin.^{28, 34, 107, 110} Intravenous administration of these preparations is preferable to injection intramuscularly, in that the latter procedure is attended with some risk of local irritation. However, mercupurin is less irritating to the tissues than salyrgan, and can be given intramuscularly (preferably in the gluteal region).³⁴ For intravenous injection it is well to use a needle of small caliber, since leakage from the vein into the subcutaneous tissues is liable to cause irritation, or even local sloughing of the skin (in the case of salyrgan). One cubic centimeter of salyrgan or mercupurin should be injected first to test the individual for possible idiosyncrasy to mercury, and then the next day a dose of 1 or 2 cc. may be given. Since the urinary output following an injection frequently amounts to six or more liters in 24 hours in cases with marked edema, the drug should be given early in the morning in order that the major diuresis may occur before bedtime. The patient should have an adequate salt balance (20 Gm. a day). A dose of similar size may be administered at intervals of a few days to one or two weeks for a period of months or even years,¹⁴⁴ if necessary. But a rest period of at least several weeks is generally advisable after a series of six injections. Because of an antagonistic action it is well not to use mercurial diuretics and morphine simultaneously.

The rectal suppositories of salyrgan and mercurin (the mercury portion of mercupurin), although somewhat less effective than the preparations administered intravenously or intramuscularly, are at times of great advantage, especially to the general practitioner in the field and in the treatment of patients whose veins are not readily accessible.^{45, 105} Each

mercurin suppository contains approximately five times the amount of mercury that is present in 1 cc of the preparation which is used intravenously. A cleansing enema should be administered early in the morning one or two hours before the suppository. Tenesmus which at times is occasioned by the mercurial preparation may be prevented by the use of an analgesic rectal suppository about seven minutes immediately beforehand. In the presence of diarrhea enterocolitis and hemorrhoids or any other rectal disorder caution must attend the use of the mercurial suppositories.

Marked albuminuria consequent to chronic passive congestion is not in itself a contraindication to the use of the mercurial compounds. However in the presence of acute nephritis with red blood cells in the urine caution must attend their use which should perhaps be limited to patients in *extremis*. Because of the danger of nitrogen retention and toxic manifestations they should not be employed in cases with chronic nephritis with specific gravity fixed about 1.020 even though the blood nonprotein nitrogen is not elevated. Particular care should be exercised in the administration of the new mercurial compounds to elderly atherosclerotic individuals especially if cachectic with a poor state of hydration. Danger lies in the extra burden placed upon the heart by the increased blood volume occasioned by the absorption of large amounts of fluid from the interstitial spaces and the fatigue produced by the passage of large quantities of urine. Also it is quite probable that the edematous fluid of elderly cardiac patients with impaired renal function may contain toxic materials possibly even large amounts of digitalis which may cause disagreeable symptoms. Excessive dehydration of the body by mercurial diuresis may cause distressing symptoms such as restlessness mental confusion and apathy sometimes progressing to coma and even death.¹⁰⁷ This syndrome—marked also by excessive thirst and dryness of the tongue—demands immediate administration of fluids and sodium chloride. It is well therefore in patients of this type to limit the dosage to 1 cc by vein or to half a suppository.

In view of the fact that the xanthines are believed to promote diuresis through increase of glomerular filtration and the mercurial preparations through diminution of tubular reabsorption the use of the two groups of substances alternately or in conjunction with one another (the xanthine by mouth and the mercurial intravenously) may prove of advan-

tage in cases with obstinate edema^{67 68 115} Also the action of the mercurial diuretics can be augmented by the administration of acid producing salts such as ammonium chloride or ammonium nitrate in dosage of 6 to 10 Gm (90 to 150 grains) daily for two or three days prior to and during the use of the mercurial preparation⁷⁸ But the necessarily large dosage of these salts even when administered in enteric coated pills of 0.5 Gm (7½ grains) each frequently causes nausea and vomiting and persistent vomiting may lead to a relative alkalosis (which tends to diminish diuresis) Usually their use is not necessary the mercurial preparation alone proving adequate but in cases with obstinate edema they occasionally are effective

OTHER DIURETIC DRUGS Ammonium chloride has diuretic properties of its own as also do ammonium nitrate ammonium sulfate magnesium sulfate, calcium chloride certain salts of potassium and urea In order to be effective by themselves in congestive heart failure these salts must be administered in very large doses which generally prove disagreeable often causing nausea and vomiting The required dosage of calcium chloride¹¹⁷ is 10 to 20 Gm (150 to 300 grains) and of potassium nitrate 6 to 10 Gm (90 to 180 grains) a day Urea in dosage of 10 to 25 Gm (150 to 375 grains) two or three times a day may be given with benefit for a period of weeks or months but it should not be prescribed when there is elevation of blood urea nitrogen^{29 63 98} At times it proves successful after other diuretic measures have failed it is particularly useful when adequate urinary output is not maintained after the removal of edema by other measures Although not pleasant to take patients soon become accustomed to it it is best given diluted in water after meals

Arsenic and bismuth¹³¹ also possess diuretic properties but are inferior to the mercurial preparations In ordinary doses such as used in the treatment of syphilis moderate diuresis occurs without demonstrable injury to renal efficiency

Parathyroid extract (parathormone) has been found of value in generalized edema associated with severe disturbance of kidney function⁹² It may therefore prove of benefit when nephritis is a complication of congestive heart failure Although it does mobilize calcium in the blood its diuretic action differs from that of calcium chloride which acts through the production of an acidosis

Diet In congestive heart failure the process of digestion generally is impaired through the circulatory stasis in the portal system. Patients are prone to suffer gaseous dyspepsia and constipation due to disturbance of the gastrointestinal tone and secretion resulting from anoxemia of the mucosa and muscularis. Not infrequently abdominal distention causes embarrassment of the heart through its displacement upward and occasionally nausea and vomiting form a serious problem. The extent of dietary restriction necessary in a given case is determined by the degree of congestive failure, the underlying etiological factors, and the patient's body weight.

In general, the diet should be adequate in caloric value to maintain the body weight at or slightly below the normal level, containing an abundance of easily assimilated carbohydrate, a relatively low amount of

FOODS TENDING TO PRODUCE FLATULENCE*

Vegetables	Sweets
Beans especially dried	All gross sweet foods as
Broccoli	Candy
Brussels Sprouts	Sugar
Cabbage	Jellies
Cauliflower	Jams
Corn	Preserves etc
Cucumber	Cheese all highly fermented
Garlic	Nuts all kinds
Lentils	Soups
Onions	Meat soups or broths
Pars fresh and dried	Vegetable stock from the gas forming vegetables
Peppers	Beverages
Potato	Carbonated water
Radishes	Highly sweetened drinks
Rutabaga	Coffee
Sauerkraut	Condiments and other foods
Swiss Chard	All condiments other than salt
Turnips	Excessively salted foods
Fruits	Spices
Apples raw	Uncooked foods
Melons especially cantaloupe and watermelon	Fried or greasy food especially cold
Raisins	

* From Treatment of Diet by C. J. Harborka, J. B. Lippincott Company Philadelphia 1931

protein, sufficient fat to meet the caloric needs, and an adequate mineral and vitamin content. The basal metabolic rate is reduced to a lower level by definite restriction of the diet and absolute rest in bed, and the heart is benefited thereby. Large meals should be avoided because of the danger of precipitating cardiac embarrassment either through gastrointestinal cardiac reflexes or abdominal distention. A light evening meal is particularly important. Carbohydrate in the form of sugars such as dextrose or lactose, honey (fructose), dextrin, malted milk, Karo syrup and foods from carefully treated cereal grains, being readily utilized for the production of energy, is of particular value to the patient with myocardial insufficiency.^{7, 119, 120} Protein for the adult patient of average size should be limited to a daily intake of approximately 50 Gm because of its specific dynamic action and the extra load which its metabolism will throw upon a damaged heart. In the presence of acute rheumatic infection with fever and especially in children, however, an abundant diet with a high protein content is necessary to combat the tendency to a negative nitrogen balance. The individual's idiosyncrasies and whims in regard to diet should be given consideration. As a rule, however, all fried or greasy foods should be avoided. Also should pork, veal, salmon, sardine, coarse cereals and breads, raw fruits and vegetables, coarse vegetables and fruits, concentrated acid fruits and vegetables, and spices and condiments other than salt. Milk and leafy vegetables in small quantities contain the necessary minerals, and orange and tomato juice provide sufficient vitamins. The quantity of sodium chloride should be restricted to that contained in the average diet as it reaches the table, only small amounts having been used in cooking the food (which is the equivalent of 2 Gm (30 grains) a day—provided the butter is unsalted and unusually salty foods are not included). A salt-free diet—which is unpalatable—is not necessary. If edema is present, the total fluid intake should be limited to 900 to 1500 cc in 24 hours.

In the presence of marked edema a semi-starvation diet of approximately 800 Calories for a few days or several weeks, the length of time depending on the patient's body weight and the response to treatment, frequently brings about improvement in cardiac efficiency and marked diuresis. (See DIET I.) The Kirell diet, which allows only 200 cc (7 ounces) of skimmed milk four times in 24 hours without other food

DIET I—GRAVE CONGESTION, ABOUT 800 CALORIES*

Breakfast (8 to 9 A M)

- (a) Bread or toast (with or without syrup or honey), 1½ oz and one cup of tea (with milk and one or two lumps of sugar), 5 oz

or (b) One raw egg in milk, 6 oz

Dinner (1 30 P M)

Minced meat or chicken, 2 oz., or fish 3 oz

Bread 1½ oz., or spinach, 2 oz

Supper (7 P M)

- (a) Custard, 5 oz

or (b) Milk pudding 4 oz

or (c) Bread and milk (milk 4 oz., bread, 1 oz. with sugar), 5 oz

Drinks in small quantities between meals Total fluids, including tea and milk in above dietary rarely to exceed 20 oz (570 cc.)

DIET II—CONVALESCENCE, WITHOUT EXERCISE, ABOUT 1500 CALORIES

Breakfast (8 to 9 A M)

- (a) Bread 2 oz

Butter, ¾ oz

One egg, poached or boiled, or white fish (not fried), 3 oz

Tea or coffee, 4 oz

Milk, 1 oz

Sugar, one to two lumps

Honey, 1 oz

or (b) Grapefruit or orange

Cereal dry cornflakes 1 oz. or cooked oatmeal, 3 oz

Milk, 5 oz

Sugar, ½ oz

Dinner (1 30 P M)

- (a) Fish white (not fried), 4 oz (or meat, chicken rabbit, mutton sweetbread or game, 2 oz)

Potato 3 oz., or bread, 1 oz

Spinach, tomato green of cabbage, peas or beans or salad 2 to 3 oz

- (b) Milk pudding 5 oz

with cooked fruit (prunes, plums, apricots baked apple)

with sugar, or raw orange peach or grapes

Tea (4 to 5 P M)

Tea, 4 oz

Milk, 1 oz.

Sugar, one to two lumps

* From Diseases of the Heart by Sir Thomas Lewis The Macmillan Company 2nd edition New York 1937

Supper (7 P M) only one course

- (a) Fish 4 oz
Potato 3 oz
- (b) Milk pudding 6 oz
- (c) Chicken 3 oz or fish 4 oz
Salad

Any of these (a) to (c) with bread 1 oz butter $\frac{1}{2}$ oz

All meals to be taken without fluids Fluids to be drunk an hour before chief meals water or for those accustomed to alcohol whisky or brandy ($\frac{1}{2}$ oz) and water not more than twice daily or once with one glass sherry claret hock with midday meal Total fluids up to 40 or 50 oz

and with but little additional fluid often proves of value but in its strict form it should not be continued for more than two or three consecutive days For individuals who dislike milk a modification of the Karell diet such as proposed by Bannick and Smith ⁴ may be substituted—the food being prepared without adding salt and water or pellets of ice being permitted in an amount which brings the total intake of

MODIFIED KARELL DIET OF BANNICK AND SMITH
Composition of Diets

Diet	Carbohydrate	Protein	Fat	Water	Calcium	Magnesium	Potassium	Sodium	Phosphorus	Chlorine	Sulfur	Iron
Karell	40	24	32	696	0.96	0.096	1.144	0.408	0.744	0.848	0.272	0.0019
Modified Karell	53	26	40	465	0.40	0.073	0.866	0.583	0.550	0.852	0.368	0.010

Breakfast

Bread (toast)	10 Gm
Ten per cent fruit (orange)	100 Gm
Sugar	5 Gm
Egg	1

Dinner

Bread	10 Gm
Cream soup	150 Gm
Butter	5 Gm

Supper

Bread	10 Gm
Milk	200 Gm
Butter	10 Gm
Egg	1

fluid in water and food to 700 cc. Chewing of gum and the sucking of lemon sour balls are helpful in the alleviation of thirst. After several days simple foods such as cereals and cream fruit juices toast with unsalted butter soft boiled eggs vegetable purees jellies and ice cream should be allowed with an increase to 1200 Calories but with the amount of fluids still limited to 900 or 1200 cc. Patients with recurring edema frequently are benefited by repeating the Karel diet or its modification every three or four days. However the danger of too rigid or prolonged restriction of fluids must be kept in mind in fact some patients respond better when a more liberal fluid intake is allowed. Occasionally just before or after surgical operation an increase of fluid intake to 1500 or 1800 cc. is permissible for clearing the urinary tract. But intravenous or subcutaneous administration of saline solution or other fluids must be carried out with caution because of the danger of precipitating or aggravating edema of the lungs and dependent edema. 2 23 46

Anorexia and nausea which at times constitute a serious problem often can be relieved by means of a more tempting arrangement of the diet. Occasionally solid foods can be retained whereas liquids cannot be. Persistent vomiting demands careful study to determine whether it is due to venous stasis improper diet overdosage of digitalis or too heroic medication. And if vomiting is severe absolute rest of the stomach is advisable only bits of cracked ice being offered sips of cold ginger ale carbonated water or iced champagne may be allowed provided the gas does not cause annoying abdominal distention. After 12 or 24 hours tea toast milk and lime water peptonized milk whey albumin water (consisting of the whites of six to ten eggs a day flavored with lemon), and strained vegetables may be added gradually. Bismuth subcarbonate or cerium oxalate in dosage of 0.6 Gm. (10 grains) by mouth one half hour before feeding may prove efficacious. In obstinate cases feeding by rectum or glucose solution by vein may be necessary.

After the stage of severe failure the caloric intake is gradually increased and the consistency of the food is changed from that of the liquid and soft to a light mixed diet of 1500 to 2000 Calories with 200 Gm. of carbohydrates 40 to 50 Gm. of protein and 100 Gm. of fat. Concentrated foods such as fish meat and eggs are usually preferable to a strict vegetarian or lactovegetarian diet bulky vegetables of low caloric yield should not be used. Tea and coffee may be used in moderation but

excessive amounts must be avoided because of the tendency to cause sinus bradycardia and premature beats and occasionally paroxysmal tachycardia. Alcoholic beverages in small or moderate amounts often have a relaxing effect and thus may aid in securing rest. Through vasodilatation alcohol also may relieve or prevent angina pectoris. The amount of smoking should be definitely limited, if not abandoned altogether. Some individuals are particularly sensitive to tobacco, experiencing premature contractions, simple tachycardia, paroxysmal tachycardia or even paroxysmal auricular fibrillation or an attack of angina pectoris and at times presenting lowering or inversion of the T waves of the electrocardiogram⁵. Also smoking may prove harmful by promoting cough and upper respiratory infection.

For patients with arteriosclerosis and arterial hypertension particularly if obese and with symptoms or signs of coronary artery disease continued restriction of the diet to 800 Calories (approximately 80 Gm of carbohydrate, 50 Gm of protein and 35 Gm of fat) or to 1200 Calories for a period of several months or longer at times proves of benefit^{90-91, 110}. But the fact must be kept in mind that the blood serum protein level tends to be lowered in congestive heart failure of long standing with marked edema⁹⁵ and that in such event a more liberal diet is indicated. When obesity is associated with congestive heart failure the diet should be limited to bring about a gradual reduction to 45 to 68 kg (10 to 15 pounds) underweight. Such procedure is of value since in obesity the function and nutrition of the myocardium is impaired by subepicardial deposits of fat, the blood capillary system and the total metabolism are increased in obesity, the action of the heart is embarrassed by displacement upward by intraabdominal fat and on exertion the work of the heart is increased through the greater expenditure of energy involved in moving the excess weight¹⁴³. Patients with coronary artery disease and diabetes requiring insulin should be given carbohydrates in amount sufficient to keep the blood sugar slightly above normal in order to avoid the danger of precipitating angina pectoris by causing glycogen deficiency of the myocardium.

Cathartics and Laxatives In congestive heart failure vigorous purgation as a routine measure is not to be recommended because of its weakening effect and the tendency to provoke gastric upset. Frequent use of the bedpan or commode is tiring—requiring effort when rest is of

CARDIAC DIET*

50 Gm Protein—1800 Calories

Quantitative and Estimated Quantitative Total Food Allowance for One Day
 Carbohydrate, 210 Protein, 50, Fat, 85, Calories, 1805

Food	Gm Weight	Household Measure
Cereal (cooked)	140	$\frac{3}{4}$ cup
Bread	60	3 thin slices
Butter	35	$3\frac{1}{2}$ squares
Salad dressing with oil		
Milk	400	2 glasses
Cream, 20 per cent	60	$\frac{1}{4}$ cup
Meat (lean)	45	1 small serving ($1\frac{1}{2}$ ounces)
Bacon		
Egg	50	1
Vegetables, 3 per cent	300	3 servings ($1\frac{1}{2}$ cups)
Vegetables 6 per cent		
Fruit, 10 per cent or 15 per cent	300	3 servings
Potato or substitute	150	2 small servings ($\frac{3}{4}$ cup)
Sugar and jam	30	2 tablespoons
Dessert	100	1 serving

Suggested Distribution of Total Food Allowance for One Day

Breakfast			Gm
Fruit, 10 per cent	. . .	1 serving	100
Cereal (cooked)		$\frac{3}{4}$ cup	140
Egg		1	50
Bread (toast)		1 thin slice	20
Butter		1 square	10
Sugar		1 tablespoon	15
Jam		1 tablespoon	15
Cream, 20 per cent		$\frac{1}{4}$ cup	60
Beverage—Coffee substitute			
Luncheon			
Meat		1 small serving	45
Potato or substitute		1 small serving	75
Vegetable 3 per cent or 6 per cent		2 servings	200
Bread		1 thin slice	20
Butter		$1\frac{1}{2}$ squares	15
Dessert		1 serving	100
Milk		1 glass	200
3 00 P M—Fruit 10 per cent or 15 per cent		1 serving	100

* From Treatment by Diet by C J Barborka J B Lippincott Company Philadelphia

Dinner

Potato or substitute	1 small serving	75
Vegetable, 3 per cent or 6 per cent.....	1 serving	100
Bread	1 thin slice	20
Butter	1 square	10
Fruit, 10 per cent or 15 per cent.....	1 serving	100
Milk	1 glass	200

prime importance. In the acute stage of congestive failure, however, 0.1 Gm. ($1\frac{1}{2}$ grains) of calomel, or 0.26 Gm. (4 grains) of blue mass (*massa hydrargyri*) in the evening, followed by a saline purgative the next morning, often proves of benefit. Compound jalap powder in dosage of 2 Gm. (30 grains) is an effective hydragogue. Half an ounce of magnesium sulfate, or some other saline preparation, such as "sal hepatica" or "Eno effervescent salt," once daily or every other day often proves helpful in getting rid of edema, especially in individuals of plethoric type. Straining should be avoided. Continued use of drugs with mild cathartic or laxative effect, such as cascara, mineral oil, agar-agar, saline preparations, or natural mineral waters (such as Carlsbad or Hunyadi-Janos water, which contains the sulfates of sodium and magnesium), may be necessary for the prevention of constipation.

Venesection: In congestive heart failure of long standing, with high venous pressure (over 15 mm. of mercury in arm vein) and edema persisting in spite of rest, digitalis and diuretics, the removal of 250 to 1000 cc. ($\frac{1}{2}$ to 2 pints) of blood by use of a needle of large bore or a scalpel is often attended with definite relief of dyspnea, venous engorgement and sense of fullness in the head. The amount of blood to be removed is determined by the habitus of the individual and the response to the procedure. Obvious anemia is a contraindication. The procedure is attended with particular benefit in plethoric individuals with high circulating blood volume, with heart failure secondary to arterial hypertension and coronary sclerosis; but its most striking value is observed in its use as an emergency measure in left ventricular failure with acute pulmonary edema—in which at times it is indeed life-saving. In all probability the immediate relief of dyspnea and other symptoms mainly results from decrease of the venous engorgement, particularly of the pulmonary circuit, and reduction of the viscosity of the blood; and it is possible that lessening of the cardiac dilatation improves the efficiency

of the heart for a period omitting the reduction in blood volume. If the venous pressure gradually returns to a high level in a period of several days (as not infrequently happens) another venesection of 250 cc ($\frac{1}{2}$ pint) may be performed a week or ten days after the first and if necessary may be repeated ten days later. However, improvement in knowledge as to the proper use of digitalis and the introduction of the mercurial diuretics have reduced considerably the need for venesection.

In primary failure of the right ventricle caused by chronic pulmonary fibrosis or emphysema the relief of subjective symptoms by venesection is not so striking as in failure of the left ventricle alone or with secondary right ventricular failure and in acute right ventricular failure (acute cor pulmonale) resulting from pulmonary embolism it might have a deleterious effect because of the fact that diminution of the volume of blood returning to the right side of the heart tends to handicap the right ventricle in overcoming the increased resistance in the pulmonary circuit.⁴¹

Paracentesis When effusion into serous cavities with disturbing symptoms persist after rest, complete digitalization, diuretic and other therapy, paracentesis is indicated. As mentioned previously, ascites generally disappears with the usual medical measures but hydrothorax tends to remain unchanged. Hydrothorax of moderate degree may augment dyspnea considerably. Removal of 500 to 1000 cc (1 to 2 pints) of fluid from the pleural cavity is usually attended with marked relief of symptoms frequently with drop in venous pressure. At times digitalis and diuretics become more effective following this treatment. Because of the possibility (though rare) of precipitating acute pulmonary edema, not more than 1,500 cc (3 pints) of fluid should be removed at one occasion. Increase of dyspnea, cough or expectoration during the withdrawal of fluid are signs for stopping the procedure.

Drainage of Subcutaneous Edema With the effectiveness of the new mercurial diuretics, drainage of subcutaneous edema by means of small cannulae inserted in the feet or legs by means of a trocar (as proposed by Soutley¹⁻³ 1877) incision in the dorsum of the foot or multiple punctures of the skin of the calf of each leg are rarely necessary. But in terminal cases—with practically no myocardial reserve—presenting obstinate edema such measures may afford temporary relief. With the patient seated in a chair with legs dependent as much as six liters of fluid can be drained in 24 hours. Large painful scrotal swelling persist

ing despite all other measures can be relieved by insertion of a Southey tube into the scrotum.

Surgical Procedures *Total Thyroidectomy* The value of total thyroidectomy in the treatment of obstinate cases of severe congestive heart failure and of angina pectoris (proposed by Blumgart, Levine and Berlin⁹ 1933) is based on the theory that the hearts of such individuals—although insufficient in meeting the demand of a normal metabolic rate—might be capable of supplying enough blood for the lessened need with a reduced basal metabolic rate. That is, relief from heart failure is gained through the substitution of myxedema. The operation does not alter the underlying cardiac pathology; it is solely a palliative measure. The procedure is to be considered only as a measure of last resort in patients with heart failure of long standing for whom life has become intolerable, all other methods of treatment having proved ineffective, yet the individuals' general physical condition must be sufficiently good to withstand the surgical ordeal. Patients with progressive myocardial lesions such as active rheumatic carditis, bacterial endocarditis, malignant hypertension, renal insufficiency, cirrhosis of the liver, recent coronary thrombosis, arteriosclerotic heart disease with progressive changes in the electrocardiogram, and syphilitic heart disease are not suitable for the operation. Also, a basal metabolic rate of less than minus ten per cent is a contraindication, since it might be impossible to lower the metabolic rate sufficiently to effect a decrease in the work of the heart.⁴⁷ In fact, there are but few cases of congestive heart failure in which the procedure is indicated; it has been found more applicable and of greater benefit in angina pectoris.

The operation calls for the highest degree of technical skill, with careful administration of anesthesia. The fall in basal metabolic rate usually is evident after the first week, attaining its lowest level of minus 35 per cent to minus 45 per cent at the end of four weeks.⁴⁷ About two months after the operation, before myxedema becomes established, thyroid extract in dosage of 0.015 to 0.03 Gm. ($\frac{1}{4}$ to $\frac{1}{2}$ grain) is prescribed each day, and continued thereafter in dosage sufficient to maintain the basal metabolic rate at about minus 30 per cent. Caution is necessary in the administration of thyroid extract because of the danger of provoking angina pectoris or heart failure through excess dosage. Rest, digitalis, and diuretics are administered whenever indicated. From a survey of the

literature and an inquiry sent to all members of the American, Southern and Western Surgical Associations, the American Society for the study of goitre, and a number of other American clinics, made by Parsons and Parks¹⁰⁷ (1937), the operative mortality in 28 patients with congestive heart failure was 10.48 per cent; excellent results occurred in 34.63 per cent; moderate improvement in 28.78 per cent; slight improvement in 2.92 per cent; and no improvement in 33.65 per cent. Postoperative pulmonary complications are a frequent cause of death.

Thoracotomy Patients with extremely large hearts, suffering precordial discomfort, dyspnea, and other distressing symptoms, at times are afforded relief through mechanical freeing of the heart by thoracotomy or resection of the ribs (precordial thiracectomy). The operation, a type of cardiolysis, consists of resection of the costal cartilage and anterior ends of several ribs, usually the left fourth, fifth and sixth, together with a portion of the sternum, being similar to that introduced by Brauer¹² for the freeing of the heart bound with adhesions of mediastinopericarditis. An anesthetic agent that can be combined with adequate oxygen is administered intratracheally with arrangement for establishing differential pressure. Postoperative complications are dangerous; therefore, great care is necessary in preparation of the patient and aftercare. The possible benefit to be derived from this procedure is limited to but few cases.

Treatment of Complications: General Surgical Operations and Anesthesia. The presence or history of congestive heart failure greatly increases the danger of complications and the mortality of major surgical procedures. Therefore, the benefit to be derived from a surgical operation must be weighed against the risk entailed. When there is dyspnea at rest with rales at the lung bases and other manifestations of myocardial insufficiency, only operations for grave emergencies should receive consideration. Whenever possible, a regimen of rest in bed with digitalization and other therapeutic measures should be enforced for several weeks or months before operation. Severe angina pectoris, recent coronary thrombosis and syphilitic aortitis add considerably to the operative risk.

When surgical operation is necessary, every effort should be made to allay apprehension. Of the greatest importance is the choice of anesthetic and its skillful administration. Any considerable change in blood pressure in either direction should be avoided. Caution therefore must

attend the use of spinal anesthesia particularly in the presence of arterial hypertension or serious coronary artery disease. If excitement can be avoided and whenever practical regional anesthesia becomes first choice. In general anesthesia the avoidance of anoxemia is important. For that reason nitrous oxide is not desirable. The best general anesthetics are ethylene cyclopropane ethylene-cyclopropane or ethylene ether. Features of importance in the conduct of anesthesia are: Proper premedication, minimal rebreathing, nicely adjusted depth of anesthesia and quick emergence.¹¹⁸ The undesirable features of ether are irritation of the respiratory tract and postoperative nausea and vomiting; it should not be selected for older individuals with chronic bronchitis. Chloroform exerts a toxic effect on the heart, liver and kidneys and therefore should not be used in myocardial insufficiency. Tribromethanol (aveutin) administered by rectum is depressing to the heart and respiration as also are the barbiturates, evipal and pentothal administered intravenously.

Cardiac standstill during surgical operation calls for the injection of epinephrine (adrenalin) hydrochloride 0.5 to 1.0 cc (1 to 1000 solution) directly into the heart and massage of the heart with the hand on the diaphragm if the abdomen has been opened. A device known as the artificial pacemaker, consisting of a needle transmitting electric impulses at the normal heart rate applied directly to the heart is claimed to be of some value.¹¹⁹

Following operation excessive gas in the gastrointestinal tract may prove distressing and at times myocardial insufficiency becomes progressively worse, the result of exhaustion or toxicity arising from a large wound area or postoperative complication. Paroxysmal tachycardia and paroxysmal auricular fibrillation not infrequently are brought on by the surgical procedure. In patients with mitral stenosis or arterial hypertension acute pulmonary edema may be precipitated and when advanced coronary sclerosis is present there is grave danger of coronary thrombosis.

The chief *noncardiac postoperative complications* of congestive heart failure are bronchopneumonia, pulmonary embolism and thrombophlebitis. Care should be taken to keep the patient warm during operation, during transfer to his room and after return to bed and after operation his head should be kept elevated for relief of dyspnea or cyanosis unless shock is present. The inhalation of oxygen after operation proves invaluable and if pulmonary atelectasis threatens the administration of a ten

per cent mixture of carbon dioxide several times daily for two or three days is of value. Coughing should be encouraged. Massage of the extremities is helpful in maintaining the peripheral circulation and in the absence of dyspnea and edema gentle passive and active movements of the extremities may be employed. In the event of massive pulmonary embolism sufficient morphine sulfate in dosage of 0.01 to 0.15 Gm ($\frac{1}{6}$ to $\frac{1}{4}$ grain) should be given to relieve pain and anxiety oxygen should be administered and papaverine hydrochloride 0.032 Gm ($\frac{1}{2}$ grain) or other antispasmodics should be given hypodermically to combat arterial spasm. But there is question as to the advisability of venesection even though marked venous distention and cyanosis of acute cor pulmonale are present.

Pregnancy Pregnancy places an additional burden on the cardiovascular system. The enlargement of the uterus occasions an augmentation of blood flow with an increase in cardiac output beginning in the fourth month and increasing until term when it is 50 per cent above normal.¹² The influence of the placental circulation upon the heart is quite similar to that of an arteriovenous fistula.¹³ In the later months of pregnancy increase in weight adds to the work of the heart and the action of the heart is hampered by displacement upward. And finally the exertion of labor is attended by increase of heart rate and elevation of blood pressure. Heart failure in pregnancy usually develops gradually after the third month tending to increase to term but occasionally it begins suddenly with auricular fibrillation or a paroxysm of tachycardia. Death may result from progressive failure acute pulmonary edema pulmonary embolism or infectious endocarditis.

The risk involved in pregnancy can be determined to a large extent by the previous functional capacity of the heart. Auricular fibrillation marked aortic regurgitation arterial hypertension and myocardial insufficiency are conditions that add a definite hazard. Women with definite symptoms and signs of myocardial insufficiency on exertion and cardiac enlargement should be warned not to become pregnant—though occasionally the desire for a child does render the risk acceptable. But patients with manifestations of congestive failure at rest should be strongly advised that the strain associated with pregnancy is much too great to be undertaken.

When a patient with slight symptoms of myocardial insufficiency becomes pregnant, the decision as to whether or not pregnancy should proceed depends on the patient's desire for a child, whether there are other children, the patient's age, whether financial status will permit sufficient rest during pregnancy, and the availability of proper obstetrical care. If allowed to proceed, the patient's course should be followed closely, with readiness to interfere if need be. She should be relieved of some of the household duties; and during the later months of pregnancy it may be necessary to spend considerable time in bed. Undue excitement should be avoided. If definite manifestations of congestive failure appear in the first few months of pregnancy, the question of emptying the uterus demands serious consideration, since not only will the patient be encountering danger from the cardiac standpoint but there is also the likelihood of miscarriage or premature labor with stillbirth. If, however, the patient is not seen until the fifth or sixth month, attempt may be made to safeguard the condition until at least the seventh month. Absolute rest in bed, digitalization, salt-poor diet and restriction of fluids frequently bring about marked physical improvement; but at times it is not well to allow progress to full term. The type of delivery is of less importance than the skill of the obstetrician and the anesthetist; and it is well to have a clinician present at the delivery. Labor should be made as effortless as possible. Cesarean section under local anesthesia (supplemented by morphine sulfate and a hypnotic such as sodium amytal or pentobarbital sodium (membital) by mouth) often is the best procedure; and in such event sterilization should be advised. Nursing should not be permitted as long as signs of venous congestion persist. Rest in bed should be continued for at least three or four weeks after the disappearance of signs of venous congestion; and then physical activities may be gradually resumed. For a review of the literature and the problems of heart disease in pregnancy the reader is referred to the monograph by Jensen.^{73a}

Treatment of Associated Diseases: *Dietary Deficiency:* Cardiac dilatation and congestive heart failure may result from vitamin B₁ deficiency—which fact is observed particularly in beriberi of the Orient. But, as Weiss and Wilkins¹⁴⁰ have emphasized, lack of vitamin B₁ may play an etiological rôle in myocardial insufficiency in any individuals with inadequate diet; it may be associated with chronic alcoholism, gastro-

intestinal disease, diabetes, drug addiction, psychic peculiarities (food fads) and poverty. Lack of vitamin C is marked with a tendency to hemorrhage which may involve the heart as well as other parts of the body. Reduction of blood protein (albumin) may through disturbed osmotic pressure lead to the formation of edema. Removal of edematous transudates causes a diminution of the tissue store of vitamins. In view of these facts, when a definite history of dietary deficiency is presented, a diet rich in vitamins and of high protein content is indicated; in the acute stage of congestive failure crystalline vitamin B₁ should be administered intravenously, intramuscularly or subcutaneously in doses of 10 to 15 mg ($\frac{1}{6}$ to $\frac{1}{4}$ gram) three or four times daily,¹⁴⁰ and after four or seven days—with general clinical improvement—the diet should have a minimum protein content of 1 Gm. per kilogram (2.2 pounds) of normal body weight, supplemented by concentrates of vitamins B and C, the total caloric intake being about ten per cent under the standard for the particular individual.¹⁰⁸

Hyperthyroidism. When hyperthyroidism is associated with congestive failure, subtotal thyroidectomy should be performed as soon as myocardial efficiency has been restored sufficiently by rest in bed and the administration of iodine, digitalis and diuretics to render such procedure reasonably safe. Iodine in the form of potassium iodide (0.3 to 0.6 Gm., or 5 to 10 grains) or Lugol's solution (1 minims, or 10 drops) three times a day for one week is essential; it promotes the storage of thyroglobulin in the follicles and holds back the flow of hormone outward from the gland, thus causing abatement of the symptoms of thyrotoxicosis.¹¹³ Iodine therapy however is seldom sufficient to control the thyrotoxicosis. With careful preparation, expert anesthesia and skillful surgery, all of which are essential for good results, remarkable benefits are frequently secured—even in cases seemingly hopeless because of heart failure. Roentgen irradiation is of value in some mild cases or in cases with persistent or recurrent postoperative thyrotoxicosis.

Hypothyroidism. In congestive failure due to thyroid deficiency (myxedema), marked improvement promptly follows oral administration of thyroid gland substance. Care must be taken, however, to avoid too strenuous dosage, especially when there is history of angina pectoris, because of the danger of precipitating a seizure through the resultant elevation of metabolic rate and increased blood flow; sudden death may

occur, even though marked general improvement and reduction of cardiac size be present. It is well to begin with a dose not greater than 0.015 to 0.03 Gm ($\frac{1}{4}$ to $\frac{1}{2}$ grain) of thyroid, U S P, daily. Digitalis should be given to relieve any symptoms and signs of congestive failure which do not yield to thyroid therapy. Very rarely is congestive failure a cause of death in hypothyroidism.

Syphilis When cardiovascular syphilis is a complication of congestive heart failure, myocardial efficiency should be restored to the best degree possible before beginning intensive antisyphilitic therapy. The use of mercury, potassium or sodium iodide or an insoluble salt of bismuth is relatively safe in comparison with that of arsenical preparations. When edema is present, a soluble mercurial compound, such as silyrgan (mersalyl) or novurit (mercupurin), may be given intravenously. After a fair degree of myocardial efficiency has been regained a course of intramuscular injections of an insoluble salt of bismuth combined with potassium or sodium iodide by mouth is started.⁹⁹ The dosage of bismuth at first is small—0.1 Gm ($\frac{1}{2}$ grains), every four or five days, and if tolerated for four or five injections without any upset, the dose is increased to 0.2 Gm (3 grains) once a week. The iodide preparation is given in dosage of 1.3 Gm (20 grains) three times a day, increasing rapidly to 4 Gm (60 grains) three times a day. Such treatment with bismuth and the iodides is continued for at least 10 to 12 weeks before any arsphenamine preparation is given. In patients with persistent symptoms and signs of heart failure at rest no arsenical preparation should be used, treatment should be limited to courses of bismuth and the iodides alternating with rest periods of from two to four months, or with courses of mercury byunction or injections of mercury salicylate (0.03 to 0.06 Gm, or $\frac{1}{2}$ to 1 grain), once a week until 0.36 Gm or 6 grains, have been administered.

If on completion of the first course of bismuth and iodides the patient still presents slight edema and dyspnea on exertion, bismarsen (bismuth arsphenamine sulfonate) should be given intramuscularly in dosage of 0.05 to 0.1 Gm ($\frac{3}{4}$ to $1\frac{1}{2}$ grains), not oftener than every five days, and later, if no reactions occur, 0.2 Gm (3 grains) every four to seven days—a course consisting of from 12 to 20 injections. But if the patient is ambulatory with only slight or no symptoms of myocardial insufficiency, intravenous administration of neoarsphenamine is begun. The initial

dose of 0.05 to 0.1 Gm ($\frac{3}{4}$ to $1\frac{1}{2}$ grains) is increased gradually at weekly intervals until the usual maximum dose of 0.3 Gm. (5 grains) is reached. A course of neoarsphenamine consists of from 10 to 12 injections. Whenever possible courses of bismuth and the iodides alternating with courses of neoarsphenamine should be continued without a rest period for at least two years. After that, one course of bismuth followed by one of bismarsen or neoarsphenamine should be given once a year for the duration of the patient's life.

The occurrence of congestive failure before the institution of anti-syphilitic treatment has an unfavorable influence on prognosis. However, properly supervised specific therapy—with adequate general medical care—does tend to retard the progress of the disease, and to alleviate symptoms and lessen disability, and may prolong life a number of years.^{99, 101}

Aftercare: The amount of rest necessary in congestive heart failure depends on the degree of failure and the response to treatment. As improvement takes place, less therapy is indicated; but the fact must be borne in mind that if digitalis was required for the restoration of myocardial efficiency it is practically always necessary to continue its use the remainder of life. Anemia should be treated with iron ammonium citrate in dosage of 3 to 6 Gm (45 to 90 grains) each day. In every case at least three additional weeks in bed are necessary after the disappearance of signs of venous congestion; and in cases of severe failure with slow recovery several months or more of rest in bed are required. It is important, however, to recognize the stage of optimum improvement in myocardial reserve, marked by the disappearance of dyspnea and edema, when gentle passive or mild active exercise will prove of benefit. In elderly individuals particularly, the lack of muscular movement associated with rest in bed is conducive to congestion in the venous capillaries; and the attendant anoxemia occasions degeneration of the tissues and toxemia, which may lead to death.⁸⁰ The patient should be kept as contented as possible with reading, games and light handwork, gradually reaching the time when he may be lifted to a chaise longue or a wheel chair for 15 minutes or half an hour. The bed and chair existence is continued until he is able to be up the entire day without fatigue, acceleration of pulse rate or dyspnea. During the latter part of this period bathroom privileges and walking about the bedroom are allowed. Climbing stairs should be postponed for at least several weeks. Patients with limited cardiac

reserve should be carried up and down stairs to enable walking on the level out-of-doors.

A careful record of the patient's weight is of value in the early detection of edema. Whenever an increase of several pounds occurs within three days, it is well to administer a diuretic, such as theophylline in doses of 0.3 Gm. ($4\frac{1}{2}$ grains) two to four times daily for one or two days, and then if edema tends to occur, rest in bed and the Karell diet on the same days that the diuretic is taken is advisable. If edema tends to recur, the patient when seated should keep his feet elevated on a stool. Though energetic treatment of latent edema it is possible to prevent the recurrence of severe congestive failure for months or years.

After the disappearance of the signs of venous congestion, benefit frequently attends a stay of several weeks or months in a sanatorium or spa—under able medical supervision—far removed from the responsibilities of business and family cares. Change of environment, pleasant surroundings, good food, and rigid adherence to certain rules of hygiene (with regular hours for rest and the proper amount of exercise) aid greatly in the rehabilitation of body and mind. A mild climate, free from the vicissitudes of late fall, winter and early spring, is most beneficial, altitudes greater than 2500 feet should be avoided; and for individuals susceptible to colds the dampness of the seashore may be attended with risk. A portion of the benefit resulting from a stay in certain well established spas arises from the pervading atmosphere of faith in its merit in the restoration of health; however, the waters of some resorts do possess certain beneficial properties. Carbon dioxide baths are of particular value in cases of advanced arteriosclerosis, and carefully graduated exercises help to improve the general circulation, and thus increase the cardiac reserve.

As recovery progresses, walking up moderate inclines, and later small hills, may be permitted, and croquet may provide diversion. But strenuous acts, such as walking far with a heavy overcoat and carrying luggage, and exciting competitive sport must be avoided. The danger which is liable to attend overexertion, fatigue and acute infectious diseases should be explained, for a single transgression beyond the limit of functional capacity may precipitate a recurrence of congestive failure. Ten or more hours of each day should be spent in bed; and lying down for a half hour or more in the daytime should be encouraged. Relaxation

should be practiced. Certain individuals with myocardial insufficiency of but mild degree eventually find it possible to spend several hours or a half day or even a greater period engaged in office or other light work. In some instances even as much as nine holes of golf on a nonhilly course may be permissible.

Psychotherapy The physician should always be of cheerful optimistic attitude. Undue apprehension on the part of the patient often may be allayed by a few words of encouragement. After the acute stage of congestive failure a definite responsibility rests upon the physician in assisting the patient in the adjustment of his life to his diminished cardiac functional capacity. The individual's psychic makeup must be understood. The need of a certain amount of physical activity for the maintenance of cardiovascular tone should be emphasized with the thought of averting a neurosis with fear of all physical exertion. In the rehabilitation of patients who fail to regain sufficient myocardial reserve to carry on ordinary activity without discomfort occupational therapy is of great importance. By learning the individual's interests much can be done toward keeping him from centering too much attention on his inability to carry on a normal active existence. Outside appreciation of his handicraft particularly in the form of some financial return provides encouragement to the shut-in individual. By keeping within their cardiac functional capacity many individuals with serious heart disease can be taught to live years of usefulness and happiness.

PREVENTION

Understanding of the etiology, pathogenesis and mechanism of congestive heart failure is essential for its proper treatment. As mentioned under *Prognosis* many of the underlying causes of heart disease do not respond to treatment and specific therapeutic measures are not available for common causative diseases such as arterial hypertension, arteriosclerosis and rheumatic fever, but many of the immediate precipitating factors are preventable and controllable. Recognition of the latter is therefore of the utmost importance for the postponement of the onset of congestive failure which should be the aim of the physician in the treatment of every patient with cardiac disease.

In at least 50 per cent of patients with congestive heart failure a definite precipitating factor can be elicited by careful clinical history.

And such cases bear a better prognosis with a greater likelihood for a more rapid and better restoration of myocardial efficiency than do those in which the onset of congestive failure occurs without any demonstrable cause entirely the result of a gradual diminution of myocardial reserve.¹²² Probably the most important precipitating factor is acute infection especially of the respiratory tract in the form of a febrile cold bronchitis influenza or pneumonia. In children the most frequent immediate cause of congestive failure is rheumatic fever. It is important therefore for cardiac patients to avoid exposure to inclement weather as also contact with individuals suffering acute colds to change wet clothing immediately and to wear woolen underclothing during the winter months. In cases with repeated reinfections from a chronic focus in the respiratory tract autogenous vaccine therapy may be tried. As cough places an extra burden upon the heart measures should be immediately directed to its relief. Another frequent immediate event in the development of congestive failure is overexertion. For example sudden violent physical effort such as running for a train may occasion the onset of failure in an individual with myocardial impairment. Other factors involving sudden additional myocardial strain are sudden rise of blood pressure psychic trauma surgical shock hemorrhage coitus overeating alcoholism and the onset of rapid heart action such as paroxysmal tachycardia and auricular fibrillation. Pregnancy and obesity also are influential factors. In all probability subclinical dietary deficiency sometimes plays an etiological role. Congestive heart failure resulting from coronary thrombosis bears a poor prognosis.

In all cases of chronic cardiac disease general measures of importance are avoidance of overexertion and nervous strain proper rest with occasional or frequent holidays a well balanced diet with avoidance of overeating avoidance of excessive use of alcohol tobacco coffee and tea and the eradication of foci of infection. Specific therapy should be instituted as soon as possible in cases of dietary deficiency anemia and syphilis and severe thyrotoxicosis and pericarditis should be treated by surgery.

After an episode of congestive heart failure recurrence with further cardiac crippling frequently can be prevented for years by the patient's living within the functional capacity of the heart continuing the use of digitalis—which usually is necessary and avoiding acute infectious diseases and other precipitating factors.

CHAPTER XXXV

LEFT VENTRICULAR FAILURE AND PAROXYSMAL CARDIAC DYSPNEA

By ALBERT W. BROMER, M.D. and WILLIAM D. STROUD, M.D.

LEFT VENTRICULAR FAILURE

Failure of the left ventricle *without* associated right ventricular failure constitutes a clinical entity of not uncommon occurrence which may result from (a) preponderant burden on the left ventricle as may be observed in arterial hypertension and aortic valve disease (b) weakness of the myocardium as occurs in coronary artery sclerosis and thrombosis and in severe anemia or (c) a combination of the two factors just mentioned as may be encountered in hyperthyroidism subacute bacterial endocarditis and rheumatic carditis. The main immediate feature of the resultant abnormal physiology is *congestion in the pulmonary vascular circuit*, with diminution of respiratory reserve *without engorgement of the systemic veins*. Dyspnea on exertion is the cardinal symptom; moist rales may or may not be present in the lung bases depending on the degree of failure and in certain cases there occur paroxysms of dyspnea at rest forming a most serious syndrome which may terminate fatally in acute pulmonary edema. As described by Welch¹⁴¹ (1878) pulmonary edema is occasioned by a disproportion between the working power of the left ventricle and of the right ventricle of such character that the resistance being the same the left heart is unable to expel in a unit of time the same quantity of blood as the right heart. In a large percentage of cases insufficiency of the right ventricle (with engorgement of the systemic veins) develops *eventually* through the increased load—back pressure—caused by the congestion in the pulmonary circuit.¹⁴⁷

In addition to dyspnea on exertion relative impairment of function of the left ventricle of moderate or severe degree with or without right ventricular failure is characterized in general by definite reduction in the vital capacity of the lungs increase in the roentgen ray shadows of the lung hilus blood vessels and increase in the intensity of the pulmonary

second heart sound ^{1 10 142} In the great majority of cases there is cardiac hypertrophy and quite commonly the presence or history of arterial hypertension. The electrocardiogram often presents left ventricular preponderance and changes in the ST complexes indicating coronary artery and myocardial disease. There is a tendency to protodiastolic gallop rhythm that is a loud third heart sound (often attended by a palpable impulse) is audible at the cardiac apex shortly after the second sound and heartbeat in the middle or even at the end of diastole when the heart rate is rapid and when the rate is slower the protodiastolic timing is more evident. In some cases the presence of pulsus alternans (which consists of alternation of strong and weak beats with normal rhythm usually detected most readily while recording the blood pressure) is additional evidence of left ventricular weakness. There frequently exists a primary organic pulmonary emphysema and bronchitis with orthopnea and at times Cheyne Stokes breathing is present during sleep.

ACUTE PAROXYSMAL CARDIAC DYSPNEA (Cardiac Asthma)

This condition consists of distressing seizures of dyspnea—caused by sudden temporary imbalance between the function of the right and the left ventricle—which are most apt to occur in recumbency at night waking the subject from a sound sleep of an hour or more but also at times developing in the daytime especially in bedridden patients or following exertion or excitement. Although in the great majority of cases the predisposing factor is preponderant insufficiency of the left ventricle the symptom complex may result from marked mitral valve obstruction ¹⁰ or any other condition which might impede the flow of blood from the lungs to the aorta. The discussion in this Chapter is limited to acute paroxysmal dyspnea due to relative insufficiency of the left ventricle the right ventricle being anatomically and functionally normal or comparatively normal.

The term *cardiac asthma* rather loosely used by various authors seems best limited to attacks of paroxysmal dyspnea in which breathing of asthmatic type is present. Bronchial spasm is usually associated with severe attacks the likelihood of its occurrence is increased by the presence of chronic pulmonary disease and in certain individuals there exists an allergic tendency, the loss of cardiac reserve and the changes incident to the attack of dyspnea being the nonspecific exciting factors which initi

ate the wheezing¹³⁵ Occasionally the differentiation between bronchial asthma and cardiac asthma is difficult

Acute paroxysmal cardiac dyspnea also must be differentiated from Cheyne Stokes respiration and evening dyspnea *Cheyne Stokes respiration* (periodic apnea and hyperpnea) occurs particularly in older individuals and is especially evident just at the onset of sleep it is caused by faulty blood supply to the respiratory center, and is not pathognomonic of heart disease but is particularly ominous when occurring during waking hours *Evening dyspnea* is respiratory discomfort which develops gradually during the waking hours attaining its maximum at the latter part of the day often preventing sleep it is not uncommon in patients with preponderant left ventricular strain and is usually accompanied by orthopnea it may occur even though the patient remains in bed and in the same position the entire day According to Harrison and his co-workers⁵⁷ (1934) it is occasioned by the increased venous return to the heart and consequent increase in the degree of pulmonary congestion resulting from the increased metabolic demands during the day as compared to the night—the relatively weak left ventricle being unable to expel the oncoming blood By sitting upright the respiratory difficulty may diminish sufficiently to permit falling asleep but—especially if the patient is overly tired and nervous—there is likelihood of being awakened after an hour or more by an attack of paroxysmal dyspnea

Incidence Acute paroxysmal cardiac dyspnea is observed most frequently in males over 50 years of age with hypertensive or coronary artery disease—with or without angina pectoris^{94 100} Coronary artery disease and hypertrophy of the left ventricle alone or in combination are always present There is considerable similarity in the underlying pathology of paroxysmal cardiac dyspnea and of angina pectoris Attacks are not uncommon that may be regarded by one observer as paroxysmal cardiac dyspnea with pain and by another as angina pectoris with dyspnea¹⁰⁰ The appearance of paroxysmal dyspnea in syphilitic aortitis⁸⁶ is not due to the syphilitic lesion in itself but to the strain on the left ventricle from arterial hypertension and insufficiency of the aortic valve⁷⁷ Not every patient with preponderant left ventricular insufficiency develops paroxysmal dyspnea a certain delicate abnormal circulatory balance is essential and also several factors must be active simultaneously in the precipitation of attacks Nocturnal paroxysmal palpitation periodic

nervousness cough and Cheyne Stokes respiration may be clinical equivalents of mild paroxysmal cardiac dyspnea and often are forerunners of severe attacks 139

The Attack An attack of paroxysmal cardiac dyspnea is characterized by a sense of suffocation causing the patient to assume an upright position—breathing rapidly—and to become restless and apprehensive breathing more and more forcibly until the attack subsides. In attacks of moderate or extreme severity the accessory muscles of respiration are brought into play the chest—expanding less and less effectively with expiration greatly prolonged—tends to become fixed in a forced inspiratory position there is a desperate struggle for breath often associated with a sense of impending death Cyanosis appears and deepens and frequently there is superimposed pallor with profuse cold sweat the chest becomes filled with moist sibilant and musical rales Finally the attack begins to subside cough develops and a small or moderate amount of frothy and usually blood stained sputum is expectorated and the patient is left exhausted The duration of an attack is usually from one half to one hour or longer During the paroxysm the heart rate is invariably accelerated the second sound over the pulmonary heart valve is accentuated by the acute vascular congestion in the pulmonary circuit and the systemic arterial blood pressure is generally elevated above the usual level Occasionally in the later stages of severe attacks semiconsciousness develops with fall in blood pressure and the pulse becoming almost imperceptible When the relative insufficiency of the left ventricle is of marked degree copious edema and hemorrhage may occur in the pulmonary alveoli and death may ensue from asphyxia or from state of shock

Precipitating Factors Attacks of paroxysmal dyspnea are precipitated through sudden intensification of the abnormal circulatory balance between the two ventricles by (a) factors that increase the demands on the heart such as a dream or nightmare occasioning emotional disturbance or physical effort noise paroxysms of cough assumption of an unfavorable position during sleep a paroxysm of arrhythmia or a prolonged period of apnea in Cheyne Stokes respiration or (b) rarely coronary occlusion Conditions which may be contributory to the onset of an attack are excessive physical or emotional activity during the day abdominal distention the urinary reflex and hot weather In the presence of *orthopnea*, slipping down from the elevated position may precipitate an

attack. Pulmonary engorgement tends to be occasioned by the recumbent position at night because of a shift to the lungs of fluid retained in the tissues in the form of physiologic edema during the daytime. Paroxysmal dyspnea therefore is less apt to occur if the patient's head is kept elevated with back rest or pillows. Also occasionally an attack may be initiated by the dyspnea occasioned by the assumption of an intolerable recumbent position during sleep—that is *trepopnea*,^{146, 147} through change in the position of the heart under the influence of gravity and consequent distortion of the large vessels in the mediastinum there results a sense of suffocation which may serve as the trigger in precipitating an attack.

In the minds of Harrison and his co-workers^{24, 55} coughing incident to the pulmonary congestion and perhaps associated bronchitis is the commonest exciting agent. Coughing occasioned by the gradual accumulation of mucus during sleep gives rise to an increase in the respiratory rate, which accelerates the return of venous blood to the right auricle and ventricle, causing an increase in pulmonary congestion and a tendency to cough thus instituting a vicious cycle which may progress to acute pulmonary edema and even prove fatal. The incidence of attacks during sleep seems to be dependent on sudden change from relative depression of the respiratory and vasomotor centers and reflexes during sleep to a state of hyperexcitability at the time of awakening. Apprehension exerts an influence on the onset and the progression of attacks being an important factor in the elevation of arterial blood pressure.

Prognosis. The prognosis in left ventricular failure without associated right ventricular failure is influenced to certain degree by the ability to control the etiological (the underlying and the precipitating) factors. (See Prognosis under Congestive Heart Failure.) Failure of the right ventricle develops eventually in a large percentage of cases.¹⁴⁷ The prognosis of acute paroxysmal cardiac dyspnea due to left ventricular failure is always grave. The majority of cases do not survive longer than two years; many die within six months of the first seizure.²⁴ Rarely does a patient become entirely free from attacks although not infrequently with the onset of failure of the right ventricle the attacks disappear but tend to recur when the peripheral circulation is restored to normal. The better the treatment the better the prognosis. The prognosis is much worse when cardiovascular syphilis is the underlying

etiological factor, or when there is associated congestive failure, aortic regurgitation or auricular fibrillation

THERAPY

Left Ventricular Failure in General: In the treatment of left ventricular failure of slight degree, characterized only by dyspnea on exertion, every measure possible should be directed to the control of the underlying etiological process and to the avoidance of overexertion, respiratory and other infections, emotional disturbances and other factors which might precipitate further circulatory embarrassment. Cough should be controlled with codeine. Anemia, if present, should receive proper treatment. Obese patients should be advised to reduce gradually to five to seven kilograms (approximately 10 to 15 pounds) below the average normal level. In the event of sleeplessness, barbiturates, bromides or chloral hydrate should be prescribed. If dyspnea on effort persists after reduction of physical activities to the minimum compatible with useful existence, the administration of digitalis is indicated. In many instances breathlessness at rest can be prevented for months or years by proper digitalization.

When dyspnea is present at rest, the patient should sleep with head elevated with pillows and knees slightly elevated by a wooden support beneath the mattress. A special bed with attached back rest and knee support is of advantage if dyspnea is of pronounced degree. Daily activities should be restricted; the evening meal should be light, and no fluid should be taken during the several hours immediately preceding bedtime. Laxatives should be used whenever necessary to prevent constipation; saline purgatives prove efficacious particularly in individuals of plethoric type. It is well to establish the habit of having a bowel movement shortly before bedtime, and the bladder should be emptied immediately before retiring. The temperature of the bedroom should not be allowed to become too warm or too cold. Patients subject to cough should be given codeine before retiring. A combination of phenobarbital and codeine sulfate, 0.03 Gm ($1\frac{1}{2}$ grain) of each, often proves efficacious. As certain sedatives occasionally favor the incidence of disturbing dreams the best preparation in a given case is determined by careful observation.

Paroxysmal Cardiac Dyspnea: In the treatment of paroxysmal cardiac dyspnea measures must be directed to the restoration of the functional capacity of the left ventricle, the alleviation of restlessness and

excitability and the relief of pulmonary vascular congestion. Mild attacks are usually aborted by the patient's assuming the upright position. Sitting upright in bed or getting out of bed to sit or stand by an open window often bring relief within a few minutes. The upright position increases the vital capacity of the lungs by improving the action of the diaphragm, diminishing the return of venous blood to the heart and lessening the possibility of edema shifting from the lower extremities to the lungs. Many attacks of moderate or greater severity also pass off spontaneously through the assumption of the upright position and the disappearance of the inciting stimulus (*viz.* fear, cough or an intolerable position) or are relieved by the administration of sedatives that reduce the irritability of the respiratory center. If an attack does not subside spontaneously and cannot be checked by the use of morphine, acute pulmonary edema is liable to occur.

Treatment of Attack. A severe attack of paroxysmal cardiac dyspnea demands prompt and energetic treatment. The patient should be placed in the upright position or bent slightly forward, either in bed supported by back rest and pillows or, if preferred, be allowed to sit on a straight backed chair or to stand with support. Morphine sulfate in dosage of 10 to 15 mg ($\frac{1}{16}$ to $\frac{1}{4}$ grain) should be administered subcutaneously immediately. By depressing the respiratory center and allaying anxiety and restlessness, morphine aids in the relief of dyspnea, suppression of cough and lowering of blood pressure. However, in patients with asthmatic type of respiration, with greatly prolonged expiration, morphine in too large dosage is liable to precipitate acute edema of the lungs through the consequent abrupt diminution of respiratory effort, through sudden removal of the previously existing backward pressure on the capillaries lining the alveolar walls, there results an increased permeability of the capillary wall.⁶ Also, in the presence of acute pulmonary edema, large dosage of morphine may prove fatal through too marked depression of the respiratory center and the consequent inability to cough up the copious serous fluid. Atropine sulfate in dosage of 0.1 to 0.6 mg ($\frac{1}{100}$ to $\frac{1}{1000}$ grain) subcutaneously may prove helpful in diminishing the bronchial secretion and moisture in the lungs and relieving bronchial spasm. Large doses are contraindicated because of the danger of resultant stimulation of the respiratory center.

Theophylline ethylenediamine (metaphyllin aminophyllin theophylline) in dosage of 0.25 to 0.5 Gm ($3\frac{3}{4}$ to $7\frac{1}{2}$ grains), administered with from 50 to 100 cc of 50 per cent glucose solution slowly intravenously proves of value through improvement of the coronary circulation and consequent increased efficiency of the left ventricle and relief of bronchial spasm. Marked reduction in the venous and intrathecal pressure following the intravenous administration of theophylline ethylenediamine has been demonstrated.⁵³ The concentrated solution of glucose is believed to improve the nutrition of the myocardium and to cause diuresis through its ability to draw fluids from the body tissues.

Peripheral venous stasis, accomplished by the application of sphygmomanometer cuffs, tourniquets, bandages or towels to the proximal portion of the thighs and arms at a pressure slightly above the diastolic blood pressure is an effective therapeutic measure.^{33, 54, 130} By trapping the blood in the four extremities the venous return to the right side of the heart is reduced with consequent lessening of pulmonary congestion and left ventricular encumbrance. The ideal apparatus consists of four sphygmomanometer cuffs connected in series attached to a manometer. The compression is continued for 10 to 15 minutes and then gradually released from one extremity at a time for one minute—to be repeated if necessary. Application for 10 to 30 minutes usually is sufficient although relief often is apparent within one to three minutes.

Venesection proves an effective measure particularly when acute pulmonary edema is present and there is evidence of peripheral venous congestion. Rapid withdrawal of 250 to 750 cc ($1\frac{1}{2}$ to $1\frac{1}{2}$ pints) of blood from a vein of the arm by phlebotomy or venipuncture reduces the venous return to the right side of the heart and decreases the viscosity of the blood. The amount of blood to be removed should be determined by the lessening of the venous engorgement and the relief of dyspnea. The effect of venesection tends to be more lasting than the relief by venous stasis. Needless to mention this mode of treatment is contraindicated if anemia is present.

In severe attacks particularly when acute edema of the lungs is present digitalis intravenously proves of benefit by increasing the efficiency of ventricular systole through direct action on the myocardium. But before its administration there must be certainty that no preparation of digitalis or its allies has been taken in therapeutic amount within the

two weeks immediately preceding. Also acute coronary thrombosis is a contraindication for this procedure. Digalen digifoline or digitan in dosage of 1 cc of a solution (specially prepared for hypodermic use) equivalent to 0.6 Gm (9 grains or 6 cat units) of whole leaf of digitalis ouabain (crystalline strophanthin) 0.3 to 0.5 mg ($\frac{1}{200}$ to $\frac{1}{100}$ grain) amorphous strophanthin 1.0 mg ($\frac{1}{60}$ grain) digitoxin 0.75 to 1 mg ($\frac{1}{100}$ to $\frac{1}{60}$ grain) or any other properly standardized preparation of digitalis recommended for intravenous use may be injected slowly in a single dose — with due consideration of the patient's size. (See Treatment of Congestive Heart Failure for information regarding Maintenance of Full Therapeutic Effects of Digitalis.)

The administration of oxygen often is attended with benefit (at times proving lifesaving) if an attack continues and particularly when acute pulmonary edema persists after the administration of morphine and possibly one or more of the other measures just described. If an oxygen mask tent or chamber is not available a nasal catheter should be employed. When acute pulmonary edema is presented a positive pressure of helium oxygen achieved by means of a closed circuit apparatus with a motor blower unit capable of maintaining a pressure as high as 10 cm of water has been found of value by Barach and his co-workers.⁶ Positive pressure exerts a direct opposing force on the external capillary wall tending to counteract the transudation of serum and to decrease the amount of blood entering the right auricle and ventricle.

In the presence of extreme arterial hypertension nitroglycerin (glyceryl trinitrate) in tablets of 0.6 to 1.2 mg ($\frac{1}{100}$ to $\frac{1}{50}$ grain) dissolved under the tongue proves of value by causing (a) dilatation of the peripheral arterioles with resultant diminution of peripheral resistance for the left ventricle to work against and a pooling of blood in the peripheral circuit with decrease in the amount of venous blood returning to the right auricle and (b) dilatation of the coronary arteries.

In attacks with pronounced bronchial spasm evidenced by asthmatic type of breathing epinephrine (adrenalin) hydrochloride in doses of 1 to 30 minims of 1:1000 solution given subcutaneously may prove of benefit by producing dilatation of the bronchi through stimulation of the terminations of the bronchial sympathetic fibers but caution is necessary in its administration. Its use is contraindicated in the presence of

angina pectoris and acute coronary thrombosis. And, even though occasionally in the presence of arterial hypertension a lowering of blood pressure instead of the usual rise follows its administration, it cannot be recommended for general use when such condition exists. Usually epinephrine is less effective than morphine or nitroglycerine. And, furthermore, theophylline ethylenediamine has been found to afford prompt relief in persistent extreme dyspnea, "status asthmaticus," after epinephrine has failed to effect benefit.⁶⁶

Pressure on the carotid sinus (the bulbous dilation of the common and internal carotid artery situated at about the angle of the jaw) may afford relief by causing a fall in blood pressure and slowing of the heart through a reflex vasomotor mechanism.¹³⁰ However, as the sensitivity of the reflex varies considerably in different individuals, the possibility of benefit from the procedure is in general quite limited.

Treatment Between Attacks: After an episode of paroxysmal cardiac dyspnea, every effort should be made to prevent future attacks by directing measures to the relief of pulmonary vascular congestion and to increasing the efficiency of the left ventricle. A regimen of rest, drug therapy, restriction of fluids and dietary measures similar to that required in congestive failure should be followed.

Rest in bed for from two to six weeks is most essential for the restoration of myocardial reserve. Elevation of the head and trunk with pillows and backrest is important, with provision such as a shoulder support and a thigh rest to prevent slipping down during sleep. The atmosphere of the room should not be cold, and high humidity should be avoided, since cold air predisposes to bronchial spasm, and occasionally unusual warmth during sleep acts as a precipitating factor of paroxysmal dyspnea. In cases of severe failure, morphine sulfate may be necessary for several nights to ensure adequate sleep. But in the presence of Cheyne-Stokes respiration, caution must be exercised in the use of morphine because of the likelihood of consequent exaggeration of the periodic breathing. If an opiate is necessary under such conditions, caffeine sodio-benzoate in dosage of 0.3 to 1.0 Gm. (5 to 15 grains) should be administered with it. Theophylline ethylenediamine in dosage of 0.25 to 0.5 Gm. ($3\frac{3}{4}$ to $7\frac{1}{2}$ grains) administered slowly intravenously with 50 per cent glucose solution just before bedtime is of value in the promotion of sleep and

the prevention of attacks. Full digitalization should be effected by the administration of divided doses with care to avoid toxic effects especially in cases with coronary thrombosis. Codeine sulfate 0.03 to 0.06 Gm ($\frac{1}{2}$ to 1 grain) and luminal sodium in doses of 0.03 to 0.06 Gm ($\frac{1}{2}$ to 1½ grains) administered alone or in combination by mouth or if necessary subcutaneously may be substituted for morphine if intolerance to the latter exists.

Several days after the attack any of the milder barbiturates, bromides and chloral hydrate usually suffice for relieving excitability and allaying apprehension. As previously mentioned, codeine should be given whenever cough is an annoying symptom. The administration of a vasodilating drug by mouth for a period of weeks often proves of benefit. For example, theophylline (theocin) 0.3 Gm (5 grains) may be given by mouth three times a day for several days and then be repeated after an interval of five days or a week, or theophylline ethylenediamine 0.1 to 0.2 Gm ($\frac{1}{2}$ to 3 grains) three to four times a day may be employed. Sodium nitrite 0.06 to 0.18 Gm (1 to 3 grains) or erythrol tetranitrate 0.03 Gm (1 grain) by mouth three times a day is of value in cases with persistent extreme elevation of arterial blood pressure. Whiskey or brandy 30 to 60 cc (1 to 2 fluid ounces) at times are efficacious in aborting an impending attack. Periodic venesection at intervals of several weeks or a month (depending on the amount of blood withdrawn) is of benefit in plethoric individuals especially when venous engorgement tends to persist. In individuals subject to trepopnea a closely fitting undershirt with large wooden spools sewed to the side to be avoided may prove of value in averting attacks of paroxysmal dyspnea.²⁴

Restriction of fluids and the administration of diuretics are important therapeutic measures even though there is but little or no obvious peripheral edema. Benefit is derived through the resultant diminution in blood volume, decrease in pulmonary congestion and possibly loss of edema from the heart muscle and from the renal parenchyma. If severe congestive failure is present the amount of fluids should be limited to 1000 to 1500 cc in 24 hours while in mild cases without peripheral edema and marked pulmonary congestion refraining from fluid intake after five or six o'clock in the afternoon aids in the prevention of attacks. The mercurial diuretics, preferably mercaptopurine or salyrgan alone or with ammonium chloride or the xanthine (purine) derivatives are indi-

cated when peripheral edema persists after rest and digitalis (See Treatment of Congestive Heart Failure for details regarding Diuretics)

Diet should consist of simple easily digestible food. Abundance of carbohydrate is desirable as it is readily assimilable and productive of energy. But in cases with low serum protein a high proportion of protein is indicated¹⁰⁸ since such condition predisposes to the development of acute pulmonary edema through the increased tendency for fluid to pass from the lung capillaries into the alveolar spaces. Obese patients should reduce gradually to 45 to 68 kg (10 to 15 pounds) underweight¹⁴³

Extensive allergic investigation—including detailed history, careful physical examination for foci of infection and skin tests—should be made in patients with attacks of paroxysmal cardiac dyspnea with asthmatic breathing which tend to persist after the usual methods of cardiac therapy. A history of asthma at some time in the past is found quite frequently or the individual is allergic and the asthmatic seizure is provoked by the illness represented by loss of cardiac reserve and the changes incident to the attack of dyspnea are the so called nonspecific exciting factors which initiate the wheezing¹³⁵. Foci of infection should be eradicated and if hypersensitivity to a foreign protein exists inoculations with the specific protein may prove helpful.

Rest in bed should be continued for a period of several weeks or months after the disappearance of signs of pulmonary congestion—the length of time depending upon the degree of failure. Time is required for the restoration of the best possible myocardial efficiency. The determination of vital capacity at weekly intervals and x-ray examination of the lungs are helpful in following the clinical course. After the stage of rest in bed careful supervision of physical activities is of extreme importance. The patient must learn to live within the limitations of the functional capacity of his heart. Overexertion, emotional upsets and acute infections must be avoided. Occasional short periods of prophylactic bed rest prove of benefit when unusual fatigue, dyspnea on effort, cough, precordial pain or any other manifestation of myocardial weakness is presented. Every effort should be made to stay the progress of the cardiac incapacity—to prevent the incidence of more severe dyspnea with acute pulmonary edema, more advanced coronary sclerosis or insufficiency of the right ventricle with consequent systemic venous congestion.

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CHAPTER XXXVI

EFFECTS OF DIGITALIS ON THE ELECTROCARDIOGRAM

By THOMAS M. McMILLAN, M.D., and SAMUEL BELLET, M.D.

Introduction In spite of its wide application, digitalis is still a frequently misused drug. Since the inadequacy of small amounts of the drug was pointed out, there has been a general acceptance of the principle of large dosage. Not always, however, is due attention paid to the precautions laid down by the sponsors of this method, and all too frequently, serious disturbances are allowed to result from digitalis. During a period of eight months the writers have seen no less than six deaths that were directly attributable to overdigitalization.

This chapter is being included in this volume with the thought of reemphasizing the fact that digitalis in large amounts can be dangerous and when used improperly, can bring about serious and even fatal responses. If large quantities of this drug are to be used, intimate knowledge should be obtained regarding the clinical symptoms and the electrocardiographic findings that mark the end of its therapeutic and the beginning of its toxic action.

That digitalis should alter the electrocardiogram is to be expected. Apart from changes in the rhythm and mechanism of the heart, alterations in the shape of the P wave, rarely change in the configuration of the Q R-S group of wave, and modifications of the T wave and S T line are among the well known effects of digitalis. Of these, T wave and S T segment changes are the most important, for they are the earliest recognizable effect of its action and occur, moreover, while the action of the drug is still a therapeutic rather than a toxic one.

I EFFECTS OF DIGITALIS ON T WAVE AND S-T SEGMENT OF ELECTROCARDIOGRAM

The influences of this drug on the T wave of the human electrocardiogram were first systematically studied by Cohn and Fraser¹ in 1913 and (1130)

later by Cohn Fraser and Jamieson² in 1915 the changes observed being first flattening and later inversion. These findings have been abundantly confirmed and universally accepted. The common conception has been that digitalis inverts the T wave proper. Recently it has been pointed out that the main effect of digitalis is on the interval between the S and T waves rather than on the T wave itself.^{3, 4} The writers have attempted to observe this point carefully and to elaborate the details of the influence of digitalis by studying its effect on the T wave and S-T intervals of 100 patients.⁵

In order to clarify and simplify the results the 100 cases studied were divided into three groups (I) Those with normal hearts (II) those with a slightly diseased myocardium and (III) those with seriously diseased heart muscle. Digitalis was administered to the patients of these three groups until the appearance of evidences of toxicity forced its discontinuance and the resulting electrocardiographic changes were analyzed.

II INFLUENCE OF DIGITALIS ON T WAVES AND S-T SEGMENTS OF NORMAL HEARTS

Normal hearts were included in these studies first because it was wished to determine whether the T wave changes of digitalis differed in normal and diseased hearts and secondly because it was felt that if characteristic and consistent changes were induced by digitalis in normal hearts the resulting T wave changes could be accepted as a standard.

In normal hearts the influence of digitalis on the T wave is remarkably consistent giving a type of T wave unlike the inverted wave seen in myocardial disease—a T wave that can be accepted as the typical digitalis T wave. We will now attempt to describe its characteristics as well as its differences from the T wave inversion seen in myocardial disease.

The effects of digitalis on the T waves of normal hearts can be traced through four fairly well-defined stages (see Fig. 1).

Stage I This consists only in a lowering of the height of the entire wave without other significant change in its shape or contour.

Stage II This consists in a depression of the line between the end of the S and the beginning of the T wave—a period of the electrocardiogram referred to as the S-T interval. In the early stages this line is concave upward its point of origin being unchanged. Later it comes to begin definitely below the isoelectric line. In this stage the T wave is

90° with the second portion of the ST line it now joins the latter at a more acute angle. As these changes progress the first impression is obtained of an inverted T wave. However, if the evolution of this change is followed through its various stages it will be seen that it consists really in a progressive depression of the ST interval and does not constitute a true inversion of the T wave. The peak of the original T can still be seen above the isoelectric line as a small somewhat altered wave but present nevertheless in its original position the TP line as in Stage III does not reach the isoelectric level immediately.

The alteration just described and called Stage IV is the maximum change that the writers have observed in undiseased hearts. An inversion of the T wave in the sense of a reversed or mirror image of the original configuration is certainly never induced by digitalis in normal hearts and probably not in diseased hearts. It is for this reason that the writers believe it to be incorrect to designate the changes produced by digitalis as inversion of the T wave. They are better called a depression of the ST interval.

The T wave that results from the maximum action of digitalis on a normal heart is specific and differs in several particulars from the inverted T wave seen in myocardial disease. The main differences lie in these facts: (1) The initial portion of the ST line begins at a point definitely lower than the upper point reached by the second portion of this line in other words the down sloping first portion is shorter than the upward sloping second portion. (2) the end of the ST period—the remnant of the peak of the T wave—is always somewhat above the isoelectric line and does not fall to the base line immediately. (3) the down limb of the T wave is either straight or concave upward it is never upward convex.

We have spoken of the T wave effects of digitalis being different from the T wave changes seen in myocardial disease. The chief difference in these two types of abnormal T waves is this. The inverted T wave of myocardial disease practically always has an upward convex ST segment the T wave of digitalis always has a straight or concave upward ST segment.

With these effects on the T wave of normal hearts before the writers as the standards of digitalis action they investigated the T wave changes that occurred in diseased hearts. It should be added that the T waves of

still an upright wave though it begins lower and consequently does not extend so high above the base line

Stage III The S T line comes off lower and in this feature is simply a progression of Stage II. The first portion of this interval though becoming less curved and tending more toward a straight line is still not directed definitely downward as in a truly inverted T wave. The latter is still somewhat upright though beginning low it rises definitely above

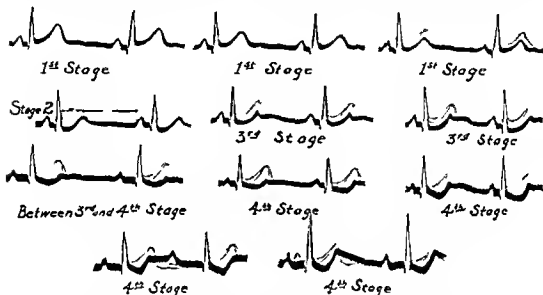


FIGURE 1. Changes in T wave brought about by digitalis. Successive changes in T waves of a normal heart under large amounts of digitalis drawn to scale. Original position and shape of T wave have been dotted in. All drawings are of Lead II. (Circulated by Medical F. & Davis Co.)

the isoelectric line. The distinguishing feature of this stage lies in the fact that after the peak of the T wave has been reached the string returns to the base line gradually, often being still somewhat elevated when the succeeding P wave begins to be written. The impression is obtained that the interval between an S wave and the succeeding P wave is divided into two parallel levels: first the slightly down sloping ST line and almost parallel but at a higher level the slightly down sloping TP line. This type of curve is regarded as characteristic of digitalis; the writers have never seen it except as a result of this drug.

Stage IV This represents a further progression of Stage III. The initial part of the ST line formerly practically horizontal now begins to point downward and instead of forming an angle of approximately

90° with the second portion of the ST line it now joins the latter at a more acute angle. As these changes progress the first impression is obtained of an inverted T wave. However if the evolution of this change is followed through its various stages it will be seen that it consists really in a progressive depression of the ST interval and does not constitute a true inversion of the T wave. The peak of the original T can still be seen above the isoelectric line as a small somewhat altered wave but present nevertheless in its original position the TP line as in Stage III does not reach the isoelectric level immediately.

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moderately diseased hearts respond to digitalis quite the same as do the T waves of normal hearts. This will not be further discussed.

III EFFECTS OF DIGITALIS ON T WAVES OF BADLY DISEASED HEARTS

The changes that result depend to a great degree upon the original configuration of the T waves.

If these waves are originally upright digitalis may affect them (1) exactly as it influences the T wave of normal hearts. Stage IV may directly result. Stages II and III are often omitted. (2) the characteristics of digitalis inversion may be entirely missing, the inversion resembling that seen in coronary artery disease (Pardee²) or ordinary forms of myocardial disease.

The usual and most commonly observed effects of digitalis on an inverted T_1 and T_2 with a bicardiogram are (1) To increase the degree of inversion. (2) to change inverted myocardial T to a digitalis type T with a characteristic upward concave ST segment or (3) to force the T wave to come off below the isoelectric line without notable change in shape. Not infrequently an inverted T wave in Leads I and II is rendered less inverted but only very occasionally (two out of a hundred cases) does this progress to the point where the inverted wave is rendered definitely upright. We have just stated that an inverted T wave may be rendered more inverted or less inverted by digitalis. The former is apt to occur when the T waves are originally slightly inverted, the latter when the inversion is deep.

In left axis deviation the T wave changes in Leads I and II are similar to those we have just described. In Lead III with left axis deviation an inverted T wave may become upright or an upright T inverted, the ST segment is often elevated.

The effects of digitalis on the T waves of normal and diseased hearts are briefly summarized in the following table.

EFFECTS OF DIGITALIS ON T WAVES IN DIFFERENT TYPES OF HEARTS

1. In normal and slightly diseased hearts the T waves are changed by digitalis to a typical Stage I, II, III or IV, never to a myocardial type T wave in which the ST line is upward convex.

2. In advanced heart disease the ultimate change depends on initial direction of T wave.

- (a) If upright or flat the T wave may be changed to a myocardial type, or to a typical Stage I, II, III or IV
- (b) If slightly inverted, the T wave may become more inverted (myocardial type T), or—
- (c) May be changed into typical digitalis waves with depressed ST intervals as seen in normal hearts
- (d) If initially markedly inverted the T wave may tend to become upright or at least become less negative or it may be made to come off below the isoelectric line without significant change in shape
- (e) Where there is a left axis deviation with T upright this wave may invert in Lead I with the initial part of T below the isoelectric line with the

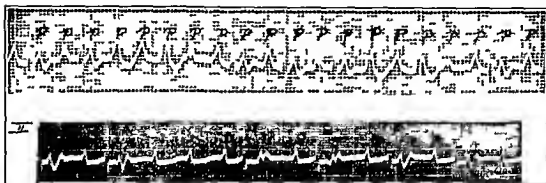


FIGURE 2 Simple tachycardia and associated A V block caused by digitalis. The top strip (Lead II) shows a sinus tachycardia with a rate of 230 that followed previous amounts of digitalis. In the lower strip (Lead II) is shown a sinus tachycardia with a rate of 120 that followed the ingestion of a single dose of 1.0 grains of the tincture of digitalis. In both cases there is an associated A V heart block. In both instances the rate subsequently returned to normal without change in the configuration of the P waves as the influence of digitalis wore off. (Cyclopedia of Medicine F. A. Davis Co.)

upright T in Lead III beginning above the isoelectric line. In other words it may resemble the type T described by Parkinson and Bedford⁷ as occurring in coronary occlusion.

When diseased hearts are considered (the only hearts to which digitalis is ordinarily administered), it is not always possible to tell whether certain altered T waves are the result of digitalis or of myocardial disease. If these waves present the characteristic changes of digitalis the influence of this drug can be positively recognized. If the T waves are of the myocardial type and show none of the characteristic digitalis effects this drug may nevertheless have brought about the change though its influence cannot be certainly identified.

However if a heart under digitalis yields a myocardial rather than a digitalis type of T it can be concluded that that heart is diseased, for digitalis causes a myocardial T wave only in seriously damaged hearts.

Not infrequently, digitalis unmasks myocardial disease by changing a normal appearing, upright T wave into a typically inverted wave, lacking entirely the digitalis characteristics. This change, too, only results in seriously diseased hearts.

Can the stage of digitalization be judged from the shape of the T wave? In normal or slightly diseased hearts, this can be done approximately, in badly diseased hearts, it cannot. Alteration of the T wave reaches its maximum while the action of digitalis is still a therapeutic one. It will not further change when the effects of this drug become toxic. In other words, it is not possible to tell by the T wave when

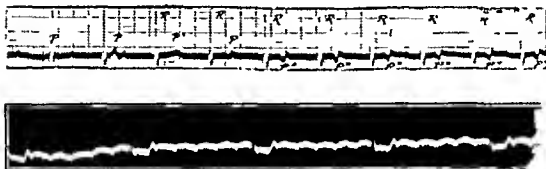


FIGURE 3. AV dissociation and AV rhythm. Atrial flutter. In the first half of the upper tracing (Lead II) is shown AV dissociation with the ventricle being driven by a nodal pacemaker more rapidly than the sinus node is driving the auricles. In the last half of the tracing the AV node supersedes the sinus node completely, controlling both the auricles and the ventricle. This mechanism was induced by digitalis on several occasions. The lower tracing (Lead II) shows an atricular flutter with high grade first block that followed severe digitalis poisoning. (Cyclopedia of Medicine I. A. Davis Co.)

digitalis ceases to exercise a beneficial effect and begins to affect the heart harmfully. However, if the T wave changes have been followed thru their entire development until their maximum has been reached, from the point of view may well be taken that a toxic digitalis action is approaching and further digitalization should be proceeded with cautiously. In diseased hearts, the zone between maximum therapeutic action and beginning toxic action is a very narrow one.

IV. EFFECTS OF DIGITALIS ON P WAVE OF ELECTROCARDIOGRAM

In addition to the T wave, the P wave is also affected by digitalis. This wave may be inverted, flattened, notched, or triphasic. For the most part, these alterations are limited to Lead I. In only three cases was Lead II involved, and in none was Lead III

In nearly all cases changes in the P wave occurred after the action of digitalis had become a toxic one. However this is not always the case occasionally minor alterations in the P wave have been seen to appear during the early stages of digitalization as transient phenomena. The effects of digitalis on the P wave are brought about in the main through vagal action they usually disappear under atropine.

V EFFECTS OF DIGITALIS ON RATE RHYTHM AND MECHANISM OF THE HEART

1 Influence on the Cardiac Rate During Normal Sinus Rhythm. Formerly slowing of the heart was thought to be one of the main effects of digitalis. It is now known that digitalis by no means consistently slows the rate of impulse formation during sinus rhythm. Slowing does occur in a percentage of cases in which the vagus is particularly susceptible but this it not to be regarded as an expected action of digitalis.

Rather than slow a sinus rate digitalis in toxic amounts at times conspicuously speeds the heart.^{10 11 12 14 15 16} Not only do these occur moderate increases of rate at times the rate rises 100 per cent or more above the original level and constitutes a real tachycardia apparently of sinus origin. Auricular tachycardia resulting from the toxic action of digitalis is illustrated in Fig. 2. A brief history of the patient from whom the lower strip of Fig. 2 was obtained follows.

CASE 1 (Fig. 2 B). A male aged 63 obviously psychopathic drank two ounces of a potent tincture of digitalis with suicidal intent. Although he vomited a portion of the drug a considerable amount must have been absorbed in view of the electrocardiographic effects that subsequently developed. The auricular rate rose to 129 per minute. The ventricular rate was much slower as a result of a fairly high degree of A-V heart block. In two days the rhythm changed a nodal rhythm and A-V dissociation appeared. A normal sinus rhythm appeared in about a week. The T waves however did not regain their normal upright configuration for two weeks.

Conspicuous increases in the sinus rate during digitalis medication are always a serious toxic effect. Even moderate increases so far as personal experience goes have resulted only when the administration of this drug is nearing a dangerous point.

2 A-V Rhythm and A-V Dissociation. A-V rhythm has been said to be induced occasionally by digitalis.^{17 18} If this diagnosis is applied

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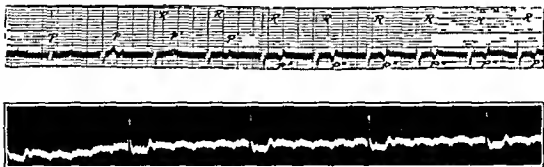


FIGURE 3 AV dissociation and AV rhythm. Auricular flutter. In the first half of the upper tracing (Lead II) is shown AV dissociation with the ventricle being driven by a nodal pacemaker more rapidly than the sinus node is driving the auricles. In the last half of the tracing the A V node supersedes the sinus node completely, controlling both the auricles and the ventricle. This mechanism was induced by digitalis on several occasions. The lower tracing (Lead II) shows an auricular flutter with high grade heart block that followed severe digitalis poisoning. (Cyclopedia of Medicine, F. A. Davis Co.)

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In addition to the T wave, the P wave is also affected by digitalis.^{8, 9, 10} This wave may be inverted, flattened, notched, or rendered diphasic. For the most part, these alterations are limited to Lead III. In only three cases was Lead II involved, and in none was Lead I affected.

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2 A V Rhythm and A V Dissociation. A V rhythm has been said to be induced occasionally by digitalis.^{17 18} If this diagnosis is applied

only when nodal impulses control both the auricles and ventricles the condition is very rarely the result of digitalis it was only twice observed by the writers (Fig 3)

AV dissociation with the ventricles responding to nodal impulses more rapidly than the auricles are responding to sinus impulses (Fig 4) is a disturbance of rhythm that is induced by digitalis fairly frequently 17 18 19 20 21 22 This disturbance is a result of digitalis has been encountered personally in 12 instances It has usually occurred only

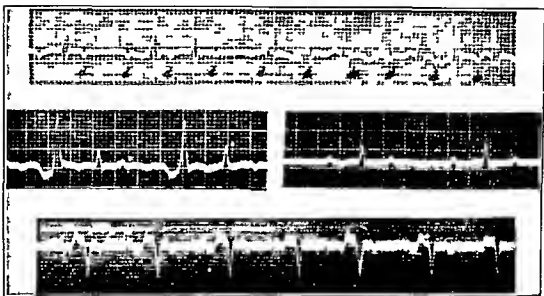


FIGURE 1 AV heart block ventricular extrasystoles and ventricular paroxysmal tachycardia caused by digitalis Strip one (Lead II) shows a total one AV heart block that followed large amounts of digitalis On the second line are shown portions of the same tracing The left strip shows two to one AV block the right completed ventricular extrasystoles In the same tracing there appeared short runs of ventricular tachycardia (not shown) At the right of the third line is shown two to one AV block with a single isolated ventricular extrasystole at the left can be seen the ending of a paroxysm of ventricular tachycardia that followed large amounts of digitalis (Cyclopedic of Medicine F A Davis Co)

after the action of the drug had become a toxic one It may be significant that aside from minor grades of AV heart block this is the only important disturbance of rhythm that the writers have been able to induce by digitalis in undiseased hearts This disturbance is normally the result of a vagal action being usually abolished by atropine While it is to be regarded as a toxic result of digitalis being chiefly vagal in origin it is not of such serious prognostic significance as other disturbances which are caused by direct action of digitalis on heart muscle

3 Auricular Fibrillation and Flutter Auricular fibrillation has been reported to follow large amounts of digitalis^{13 23 24 25 26} Auricular flutter apparently also can be produced by this drug Wedd²⁷ has reported one example and the writers²⁸ have more recently recorded two instances of this latter association (Fig 3)

A brief history of one case follows

CASE 2 (Fig 3 B) A male aged 60 with arteriosclerotic heart disease and congestive failure presented a normal sinus rhythm on admission On the sixth day after a total dose of nine drams of the tincture of digitalis had been given flutter with a 6:1 A-V heart block appeared Although digitalis was stopped this patient developed on the following day a complete A-V heart block Flutter persisted and death occurred two days after its first appearance It is interesting that at no time did the patient vomit

Though it is somewhat difficult to establish beyond doubt that fibrillation and flutter result from digitalis, it seems highly probable that this is so not only because of the clinical evidence but also because of certain established experimental facts which will not be considered here In those personal cases in which fibrillation and flutter were apparently induced by digitalis the response occurred only after the heart had been seriously poisoned by the drug

4 A-V Heart Block Prolongation of A-V conduction time (and even higher grades of A-V block) is one of the well known results of digitalis This effect has been said to be a constant and early sign and therefore of value in determining the degree of digitalis action This is unquestionably true when the auricular mechanism is fibrillation When a normal sinus rhythm is present delay in A-V conduction is not readily induced by digitalis except after large amounts have been administered In a series of 59 cases with sinus rhythm to whom massive amounts of digitalis were administered only 30 showed any lengthening of the P-R intervals of the electrocardiogram Varying grades of A-V block induced by digitalis are shown in Figs 2, 3 and 4 Slight and transient lengthening of A-V conduction time is not to be interpreted necessarily as an indication for discontinuing the drug a definite and constant lengthening should be so interpreted Dropped ventricular beats and high grades of A-V block result only from large amounts of digitalis When these

are seen, the heart has unquestionably been dangerously poisoned by the drug.

5. *Relation to Extrasystolic Disturbances:* When extrasystoles are present in diseased hearts, they can be abolished at times by digitalis 29, 30. On the other hand, there is no doubt that digitalis often induces extrasystoles in a diseased heart 31, 32, 33, 34, 35, 36. This disturbance, in its characteristic form of a bigeminal rhythm, is one of the characteristic signs of a toxic digitalis action (Fig. 4). Extrasystoles actually occur in only a small percentage of the cases to whom digitalis is administered even in toxic amounts. The writers have never observed this disturbance in normal hearts, or slightly diseased hearts that have been receiving digitalis. Moreover, it was observed in only 13 of 34 severely diseased hearts to whom toxic amounts of digitalis were administered. However, when digitalis is being used in large amounts, the appearance of isolated extrasystoles, hitherto not present, is an evidence of a serious toxic state of the heart muscle and is a positive indication for the immediate discontinuance of the drug. If the appearance of isolated extrasystoles is disregarded and the administration of digitalis persisted in, ventricular paroxysmal tachycardia or some other serious toxic rhythm will very probably soon appear.

6. *Ventricular Paroxysmal Tachycardia:* There can be no doubt that this disturbance can be brought on by overdigitalization 14, 15, 16, 25, 34, 35, 36. Aside from clinical experience, the well known ability of this drug to cause ventricular extrasystoles, and the close relation of these to ventricular paroxysmal tachycardia, strongly suggest a causative relationship between digitalis and this arrhythmia. In addition to a number of questionable examples, five definite instances have been seen by the writers in which ventricular paroxysmal tachycardia resulted almost certainly from digitalis (Fig. 1).

The history of the patient, whose tracing is shown in the bottom strip of Fig. 1 is briefly reported

CASE 3 (Fig. 4 C). A man, aged 55, with hypertensive heart disease and congestive failure was put upon 1½ drams of the tincture of digitalis daily. On the ninth day, an irregularity was observed; the electrocardiogram at this time showed numerous ventricular extrasystoles, many of which were coupled. Although the drug was stopped, this patient developed a short paroxysm of ventricular tachycardia on the following day.

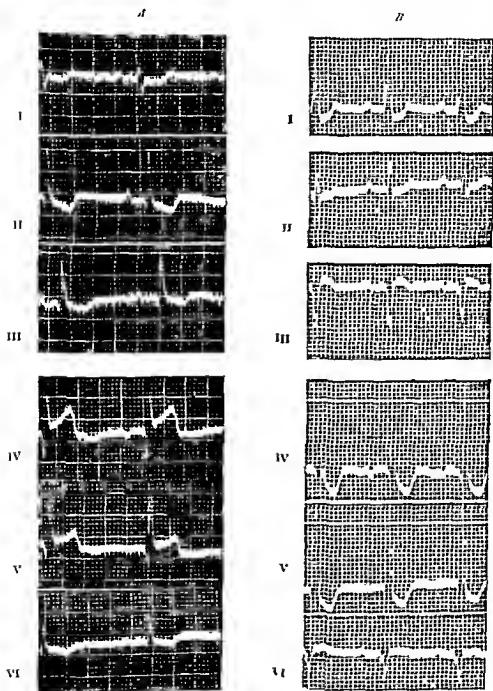


FIGURE 5
(Cyclopedia of Medicine, F. A. Davis Co)

In 24 hours fortunately the ventricular tachycardia disappeared while this patient survived the attack of ventricular tachycardia the presence of the arrhythmia is a serious event. Many patients manifesting such evidence of digitalis toxicity die soon after its appearance.

In this and the other four cases referred to isolated extrasystoles had been seen but in spite of them digitalis had been continued after their appearance. These five cases again illustrate how slight is the margin of safety between a therapeutic and toxic action of digitalis in seriously diseased hearts. In all of these cases this serious disturbance began very soon after the appearance of isolated extrasystoles and before the usually looked for symptoms of overdigitalization (nausea vomiting etc) were seen.

In conclusion it can be said that simple tachycardia A V rhythm and A V dissociation auricular fibrillation and flutter A V heart block ventricular extrasystoles and ventricular paroxysmal tachycardia can all result from digitalis. When they appear they are an evidence that the action of digitalis has gone beyond the point of optimum therapeutic benefit and has become a toxic one.

VI EFFECTS OF DIGITALIS UPON THE ELECTROCARDIOGRAM OF PRECORDIAL LEADS*

In view of the established value and general use of precordial leads it becomes essential to determine the effect of digitalis upon the complexes in these leads. This is all the more important because the changes produced by digitalis very closely simulate those produced by myocardial infarction.

The chief changes observed are those involving the R S T segment. Whereas the changes observed in the indirect leads have been divided into those observed in normal and diseased hearts this type of classification is not so applicable to the precordial leads. The types of changes observed depend upon (1) whether one is dealing with a Lead IV with

* The technique in taking the precordial leads here referred to consists in placing the right arm electrode in the region of the apex of the heart the left arm electrode at the angle of the left scapula the left leg electrode being kept in its usual position. The anteroposterior lead is referred to as Lead I IV the apex left leg lead is termed Lead V and the posterior left leg lead is called Lead VI. Recently as described elsewhere in this book the Brit. and Amer. can. Heart Associations have adopted a different method of placing the electrodes. By this newer method Lead VI is entirely eliminated and the direction of the waves is reversed. Instead of an initial deflection of the Q R S complex being normally downward it will be upward. The T waves will be upright instead of inverted.

a ventricular complex having a large initial downward deflection or (2) a small or absent initial downward deflection

1 **Changes in the R S T in Association with a Large Initial Downward Deflection** When this configuration is present digitalis will elevate the R S T segment in Leads IV and V (Fig 5) The elevation in Lead IV is usually greater than that in Lead V This is due to the fact that Lead V is approximately the algebraic summation of Lead IV and Lead VI and the S T is slightly depressed in Lead VI The one exception to this is in cases where the R S T is elevated in Lead VI due to the presence of a left axis deviation In such cases the R S T elevation caused by digitalis will be greater in Lead V than in Lead IV

2 **Deviation of R S T in Association with Small or Absent Initial Downward Deflection** The initial downward deflection is diminished in amplitude under the following conditions (1) When the anterior electrode is moved upward along the left ventricular border to the third interspace (2) in cases of myocardial disease involving the left ventricle (e g, in hypertension, luetic heart disease) (3) in old anterior occlusion the initial downward deflection may be small or entirely absent When the initial downward deflection is small in Leads IV and V as a result of any of the above conditions digitalis produces a depression of the R S T segment below the isoelectric line resembling very closely that seen in Stage IV of digitalis effects observed in the indirect leads (Fig 5 B)

The differential diagnosis between digitalis effects in precordial leads and those due to myocardial infarction may be made by a consideration of the R S T alterations in the indirect leads together with the changes observed in the precordial leads While the differential diagnosis may be made in most cases in a few instances this is impossible by electrocardiographic findings alone

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CHAPTER XXXVII

SURGERY OF THE HEART AND PERICARDIUM

By CLAUDE S. BECK, M.D.

Introduction: The application of the aseptic principle which was introduced some 60 years ago marks the beginning of modern surgery. Sepsis and secondary hemorrhage were banished by the aseptic methods and the dread of operation began to disappear after these methods were introduced. A great development in surgery took place in a relatively short period of time. All parts of the body were explored. The chest presented special problems which delayed the development of thoracic surgery. Who of the surgical pioneers living in the early aseptic period desired to remove a lung when the appendix, uterus, gallbladder, breast, kidney, thyroid, etc., were more accessible! Who, also, desired to operate upon the heart—an organ that is always in motion—possessing a great capacity for hemorrhage, and possessing also a constant threat of stopping! It is not surprising then to find a comment of this nature from Billroth, the pioneer in gastric surgery, made in 1883, as follows: ‘The surgeon who would attempt to suture a wound of the heart would lose the respect of his colleagues.’ Wounds of the heart were considered to be necessarily fatal. This was the general belief for many centuries. The first experiments on cardiac wounds that I can find in the literature were carried out by Block on rabbits in 1882. He produced stab wounds of the heart, successfully sutured the wound and advocated suture of the wound when the human heart was stabbed. In 1895 Del Vecchio demonstrated the healed scar that followed a wound that he had made in a dog’s heart. His demonstration was made before the Eleventh International Medical Congress at Rome and it attracted attention. Shortly thereafter, September 4, 1895, the first operation on the human heart was performed by Alex. Cappelen of Christiania. Thus the heart entered the domain of surgery.

Cappelen’s Case A man, aged 24, received a stab wound in the fourth left interspace in the midaxillary line. He walked home bleeding

from the wound. About an hour later he was admitted to the hospital at which time he showed signs of hemorrhage, an imperceptible pulse and distant faint heart sounds. Bleeding from the wound had ceased. Camphor stimulated the heart so that the pulse could be felt and con-



FIGURE 1 Alex Cappelén (1858-1919) performed the first operation upon the human heart

sciousness returned. There was dullness to percussion over the left side of the chest.

At operation chloroform anesthesia was used. The third and fourth ribs on the left side were resected. The intercostal artery was not cut. The left pleural cavity contained 1100 cc of blood. The lung was not

injured. Bleeding continued from the depth of the operative field and an opening in the pericardium large enough to admit the tip of the finger was found. The pericardium was distended with blood. It was opened. A wound in the left ventricle 2 cm long was sutured with chromic catgut and a bleeding coronary artery was ligated. The rhythm of the heart was regular throughout the operation.

During the postoperative period which lasted two and one half days the pulse was rapid, cyanosis was present and there was a slight fever. The cause of death was anemia and pericarditis. The wound had not penetrated into the cavity of the left ventricle. The bleeding had occurred from the coronary artery.

Classification of Heart Diseases. Diseases of the heart can be divided into an intrinsic group and a smaller extrinsic group. The intrinsic structures of the heart that become the seat of disease consist of muscle, valves, endocardium, epicardium, conduction system, coronary arteries and coronary veins. Which of these intrinsic structures can be treated by operation after becoming involved by any of the pathological processes? The surgical group of intrinsic lesions consists of trauma with its accompanying hemorrhage, stenosis of valves, sclerosis of coronary arteries, spontaneous rupture of the heart, aneurysm of the heart, ventricular standstill and ventricular fibrillation.

Extrinsic lesions of the heart disturb function by compression, angulation or rotation. In my experience these disturbances occur as entities. Thus a compressed heart is not also angulated or rotated and an angulated heart is not also compressed. Traction upon adjacent structures through adhesions to the heart is not included as a component of extrinsic cardiac lesions. In my experience it is doubtful whether traction in the long axis of the heart can disturb cardiac function.

As a rule an extrinsic lesion does not extend into the heart and become also intrinsic. A heart with an extrinsic deformity is to be considered as a good heart that has become crippled by an outside factor. It follows from this that if the extrinsic factor can be removed the heart becomes normal. This statement is essentially correct although there are exceptions to it. Likewise it can be stated that intrinsic disease as a rule does not become extrinsic. The adhesions that develop in rheumatic heart disease or over a myocardial infarct, both originating from intrinsic diseases, do not disturb cardiac function.

These statements originated by the writer, are the result of experiences in experimental heart work. They should help to remove the confusion that now exists in nomenclature and diagnosis. They should make the operation become a logical procedure. They bring into question the soundness of the Brauer operation.

COMPRESSION OF THE HEART

Physiology Under normal conditions the pressure upon the heart and the great vessels at the base of the heart is negative or less than the pressure of the atmosphere. This negative pressure is produced by the elastic recoil of the lungs and measures 4 to 6 cm. of water. Likewise the pressure within the *venae cavae* is negative by several centimeters of water. The walls of the *cavae* are soft and collapsible and readily yield to pressures from within or from without. Let us consider the effect of an increased pressure in the pericardial cavity such as occurs when the heart is stabbed and bleeding takes place from the wound. As the heart and intrapericardial segments of the *venae cavae* are compressed by the accumulated blood we find that the *venae cavae* and the right auricle become collapsed. The flow through these structures is immediately reduced and the blood is held back in the venous system. The venous pressure immediately begins to rise and if it can rise sufficiently high to overcome the collapsing effect of the intrapericardial blood filling of the heart is resumed. If additional bleeding occurs so that the intrapericardial pressure is again increased we find that a repetition of events takes place namely slowing or stopping of the blood stream in the *cavae* and elevation of venous pressure. It is apparent that a definite relationship exists between the pressure outside and the pressure inside the *venae cavae*. There are certain limits above which the pressure outside the *cavae* cannot rise and these limits are determined by the heights to which the venous pressure can rise. In acute conditions the venous pressure can rise to 15 or 20 cm. of water. In chronic conditions the venous pressure can rise to 42 cm. of water. Acute and chronic pressures above these respective levels can be considered as fatal.

The amount of pressure that the heart and *venae cavae* can tolerate depends upon several factors. One of the factors that determines the amount of pressure that can be tolerated is the rapidity with which the pressure is built up in the pericardial cavity. If it develops slowly it can

go up to levels that are definitely higher than if it develops rapidly. These higher chronic pressures are made possible because in the chronic conditions the venous pressure rises to higher levels than it does in patients with acute compression.

Two factors help to elevate venous pressure in the chronic diseases. One is an increase in the circulating blood volume. The other is an increase in venous pressure produced by the waterlogging of the body. An interesting observation that we made relative to venous pressure in patients with chronic compression was that the venous pressure fell when large quantities of fluid were removed from the abdomen. This was due to the relaxation and engorgement of venous channels in the abdomen after the abdominal tension was released. An abdominal binder restored venous pressure to its higher levels. Other points of therapeutic value along this line can be mentioned.

It is well to remember that venous pressure can be raised by the addition of fluid intravenously and that pressure upon the heart can be reduced by the aspiration of fluid from the pericardial cavity. In those cases demanding urgent treatment these procedures are of value while preparations for operation are being made. It should be noted that an elevated venous pressure is essential in cases of compression. However, after the compression agent has been removed the high venous pressure becomes something of a danger in that it dilates the heart.

In one of my patients the heart failed after a compression scar had been successfully removed. The heart dilated and failed. In certain cases showing very high venous pressures, bloodletting is sometimes indicated after the compression lesions are removed by operation. This will reduce venous pressure and will lessen the degree of dilatation of the heart.

The compressed heart is always a small heart. It cannot dilate. It cannot undergo hypertrophy. It is an efficient organ and does not waste energy. It receives a subnormal quota of blood and it pumps out a subnormal quota of blood. In pumping out a subnormal quota of blood it performs a subnormal quota of work. The heart can do nothing about the reduction in work load. It plays a passive role and receives whatever blood the venae cavae can deliver to the cardiac chambers. Inasmuch as the work load of the heart is reduced the heart muscle undergoes atrophy. The heart muscle undergoes disuse atrophy in exactly the same way as any other muscle in the body undergoes atrophy when it is not allowed

to perform its full normal function. Roberts and Beck recently showed that the measurements of the heart muscle fibers in the compressed heart were smaller than normal. The entire muscle-mass of the compressed heart is less than that of the normal heart.

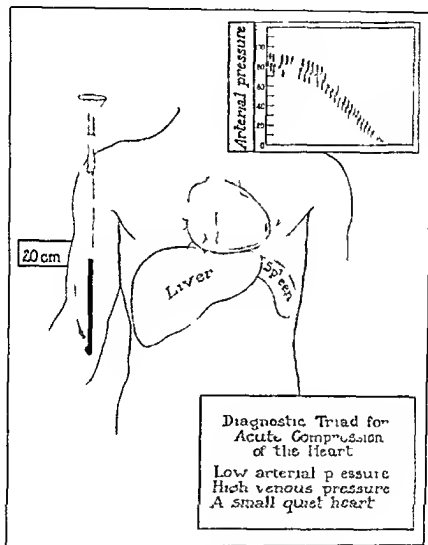


FIGURE 2. Triad for acute compression of the heart

Acute Compression Triad Acute compression of the heart is produced always by a fluid agent such as blood, pus, gas, transudate, or any combination of these. The fluid is either in the pericardial cavity or in the mediastinum. Stab wounds of the heart or great vessels are a common cause of compression. It occurs also in purulent pericarditis and it can occur as a complication following an operation in the mediastinum.

A triad of signs has been formulated by the writer for the diagnosis of acute cardiac compression. The triad consists of a small quiet heart, a falling arterial pressure and a rising venous pressure (Fig. 2). All other manifestations are secondary to these. Such secondary manifesta-

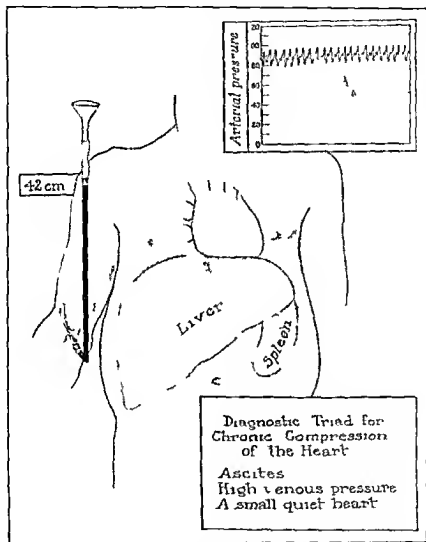


FIGURE 3 Triad for chronic compression of the heart

tions are distant heart sounds, absence of precordial pulsation, dyspnea, excitement followed by unconsciousness, cold clammy skin, and fever in the presence of infection.

The treatment depends upon the lesion producing compression. In the traumatic cases the blood clot should be removed and the injured structure repaired. In the infected lesions the pus should be evacuated.

Chronic Compression Triad Chronic compression of the heart can be produced by a variety of lesions. Compression by the formation of scar tissue around the heart and in the parietal pericardium is the commonest cause. Blood, pus, transudate or exudate in the mediastinum or pericardial cavity can produce chronic compression. Neoplasms, localized abscess, bands of scar tissue over the auricle or ventricle can produce the compression syndrome. Adhesions to the heart never produce chronic compression.

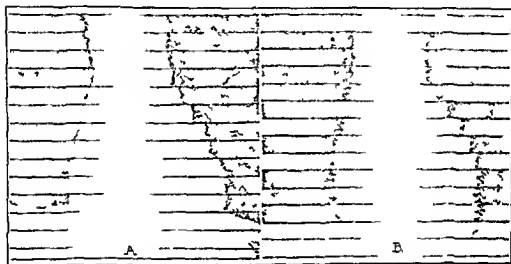


FIGURE 1. Reproduction of kymograph roentgen gram in patient of Fig. 11 with general red cardiac compression due to scar. The serrated outline indicates the amplitude of pulsation. The roentgenograms are taken with a lead grid containing true verticals in front of the plate. The plate moves during the exposure so that every phase of systole and diastole is recorded on the plate. *A*, Before operation; *B*, After operation. Note the increase in amplitude of pulsation after operation.

A triad of signs has been formulated by the writer for the diagnosis of chronic cardiac compression. This triad consists of a small quiet heart, a high venous pressure as measured in a vein of the arm, and ascites together with a large liver (Fig. 9). This diagnostic triad cannot be wrong. There should never be any confusion or mistake in making this diagnosis. No special tests are necessary. Indeed the diagnosis can be made by simple observation of the patient. The presence of cyanosis of the hands, lips, ears and face, and the prominent veins in the neck and arms point to stasis in the superior vena cava. The next observation is of the abdomen. Ascites points to stasis in the inferior vena cava. The precordium is next observed and if there is no visible pulsation present

the patient has chronic compression—not constrictive pericarditis, not adhesive pericarditis not Pick's disease, not Concato's disease, not mediastinopericarditis. These terms are confusing. While the diagnosis of chronic cardiac compression can be made by simple observation alone, it does not tell the nature of the anatomical lesion producing the compression. The lesion must be determined by additional data. A very large pericardial shadow in the x ray indicates fluid in the pericardial cavity and the fluid can be blood, pus, transudate or exudate. A smaller shadow indicates a compression scar and an asymmetrical shadow indicates a neoplasm, a dermoid cyst or a localized abscess.

The secondary manifestations of chronic cardiac compression consist of subcutaneous edema which may not be marked, hydrothorax of variable amount, a venous pressure measuring 18 to 42 cm. of water, dilated veins, cyanosis, elevated cerebrospinal fluid pressure, decreased circulation time, increase in circulating blood volume, distant heart sounds without murmurs, pulsus paradoxus, auricular fibrillation, auricular flutter or a normal mechanism, reduction in amplitude of the heartbeat, pulse pressure of about 20 mm. of mercury, reduction in cardiac output to as little as 22 cc. per beat in an adult, slurring and low voltage of the electrocardiogram, weakness and malnutrition. Fixation of the heart and fixation of the electrical axis are not important for diagnosis. Reduction in amplitude of the heartbeat can be shown by the kymograph roentgenogram (Fig. 4).

TRAUMA

PENETRATING WOUNDS OF THE HEART

These are stab wounds and bullet wounds. Any of the component structures of the heart can be injured—auricular or ventricular wall, interventricular septum, coronary arteries and veins, the conduction system, any of the valves, the great vessels at the base of the heart, and the parietal pericardium. A foreign body can enter the heart through the skin, through the esophagus or through the vena cavae or pulmonary veins. Infection can be carried in from the outside. A thrombus can form in one of the cardiac chambers at the site of the wound. The thrombus can be swept into the lung or into the peripheral circulation. Hemorrhage can occur from the heart or from the great vessels. If the blood escapes from the pericardial cavity into the chest or into the mediastinum or to the outside, exsanguination can occur. Compression of the heart

is produced if the blood does not escape and remains locked in the pericardial cavity.

The functional disturbances produced by cardiac trauma are dependent upon the structure or structures involved in the trauma. A septal lesion involving the bundle of His can produce heart block. If a leaf of the mitral valve is severed or if one of the chordae tendineae is severed, mitral insufficiency results. If a stab enters a cardiac cavity, bleeding may or may not occur. If the wound is small and enters obliquely into the ventricle, the wound will not emit blood. If a major coronary artery is severed, the ventricular wall supplied by the artery becomes ischemic and ventricular fibrillation occurs.

Diagnosis: The manifestations of penetrating cardiac injuries are variable. The clinical signs can be grouped as follows: (1) Those produced by injury of the intrinsic structures of the heart, such as a valve, a coronary artery, the conduction system, etc.; (2) those produced by exsanguination, and (3) those produced by compression of the heart. Severe injuries of intrinsic cardiac structures, as a rule, are immediately fatal and the problem of diagnosis is not presented. Generally in such accidents the ventricles are thrown into fibrillation and death is immediate. If the injury to the heart is less severe, the patient will continue to live after the accident and the problems of diagnosis and treatment are presented. In many of these patients the heart will show no evidence of intrinsic cardiac damage. The signs are entirely those of exsanguination or compression. The blood escapes into the pleural cavity, into the mediastinum, into the pericardial cavity, or through the wound to the outside. The signs of exsanguination need not be discussed.

Treatment: Only brief discussion of this subject can be given. Most of the patients who reach the hospital alive require operation. Occasionally, a patient with a stab wound recovers without operation. The body must be kept warm. If the circulation has stopped or if it is feeble, intravenous fluid should be given while preparation for operation is made. If the respiration has stopped and if the patient has lost consciousness, urgent heroic steps should be taken.

It takes but a few moments to expose the heart and release the compression. When the patient begins to breathe, an anesthetic must be given while the surgeon takes care of the wound. For the less urgent operations an anesthetic is given before the operation is started and

mechanical respiration is an added safeguard. An exposure to the left of the midline is usually used. If the wound is in the right side an exposure to the right of the sternum is indicated. The pleural cavity is opened if necessary. The pericardium is opened and the blood clot is evacuated. This releases the compression and immediately the heart fills with blood.

The first pulsations of the heart after release of the compression are more vigorous than normal and the risks of controlling the bleeding and

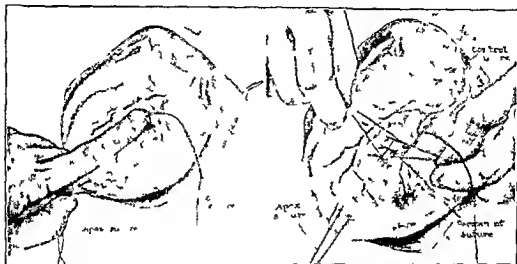


FIGURE 5 Author's method for suture of stab wound of the heart. A suture is placed in the apex of the left ventricle. This is held in the left hand and at the same time the left index finger is placed upon (not in) the wound. This stops the bleeding. Sutures are placed on each side of the wound, the finger is removed and when this is done gentle traction is applied to these sutures to control bleeding. The wound is then sutured.

repairing the wound must be met by the surgeon. The literature contains dramatic descriptions of the blood spurting of the surgeon getting it in his eyes, of a foam rising up to cover the heart, of the patient regaining consciousness and moving on the table, of tearing the heart muscle when the wound was plugged by a finger, of sutures tearing through the heart muscle, of exsanguination, of a life saved or a life lost.

The problems difficult as they appear to be, can always be managed with satisfaction if a few facts are held in mind. Hemorrhage from a ventricle must be controlled by placing a finger upon and never in the wound. To keep the finger from slipping off the wound the heart is steadied by a suture in the apex. After the apex suture is placed and after the index finger is placed upon the wound the urgency of the

operation is over and time can be taken to carry out a satisfactory repair of the wound. Control sutures are placed on each side of the finger, crossed and held under moderate tension by the assistant. The finger is removed. There is no bleeding and permanent sutures are placed. The control sutures and the apex suture are removed (Fig. 5).

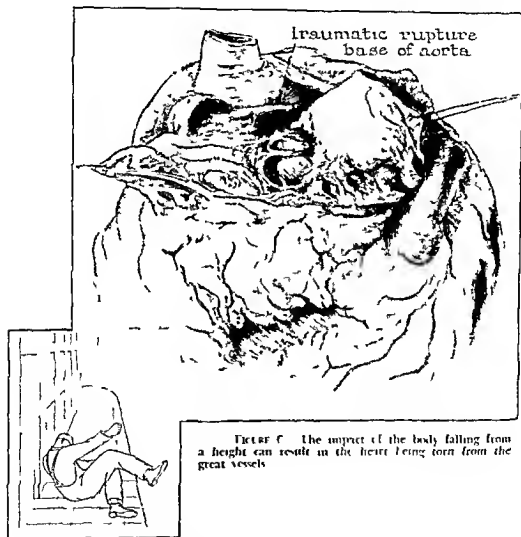


FIGURE 6 The impact of the body falling from a height can result in the heart being torn from the great vessels

An auricular wound cannot be controlled by this method. It can be repaired easily by taking the margin of the wound in clamps bringing the margins together and then suturing the wound. It is impossible to stop bleeding from an auricular wound by placing the finger upon the wound. A hemostat will crush and break ventricular wall but will not do this to auricular wall.

Complications such as foreign bodies and infections will not be discussed

NONPENETRATING WOUNDS OR CONTUSIONS OF THE HEART

These wounds are inflicted when the body falls from a great height (Fig 6) or when an impact or heavy force is applied to the chest (Fig 7)

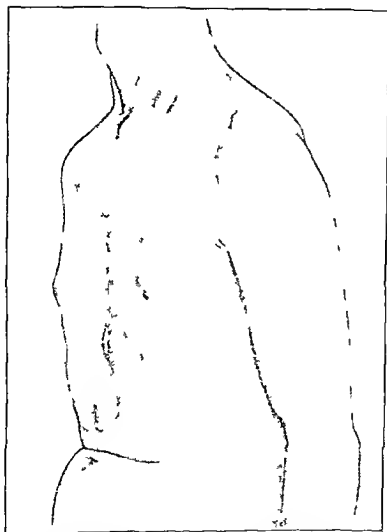


FIGURE 7 Cardiac contusion with fractures. Butted by a bull

or upper abdomen. The commonest type of injury producing contusion of the heart is the steering wheel accident (Fig 8). Another type of injury producing contusion of the heart is the passage of a wheel over the chest or over the upper abdomen (Fig 9) an impact by a fist by a

golf ball or by a horse's hoof (Fig 10) can produce a contusion of the heart. Any part of the heart can be bruised; any of the chambers can be ruptured and any of the valves can be torn. Hemorrhage of variable

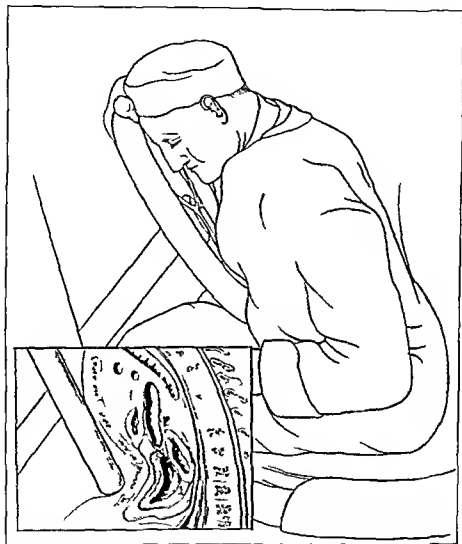


FIGURE 8 The steering wheel accident. When the speeding automobile collides and comes to an abrupt stop, the body is hurled against the steering wheel. The vertebral column moves toward the sternum and carries the heart ahead of it. The heart is impinged between sternum and vertebral column.

degree occurs in the heart muscle when a contusive injury is received. Areas of hemorrhage, contusion, and laceration may occur not only at the site of trauma but elsewhere in the heart. These areas of hemorrhage can be multiple. The heart can be bruised without fracture of sternum.

or ribs. Indeed, there may be no demonstrable evidence of injury to the chest wall.

Rupture of the heart can occur in several ways. It can be ruptured as a toy balloon can be ruptured in one's hand by the application of

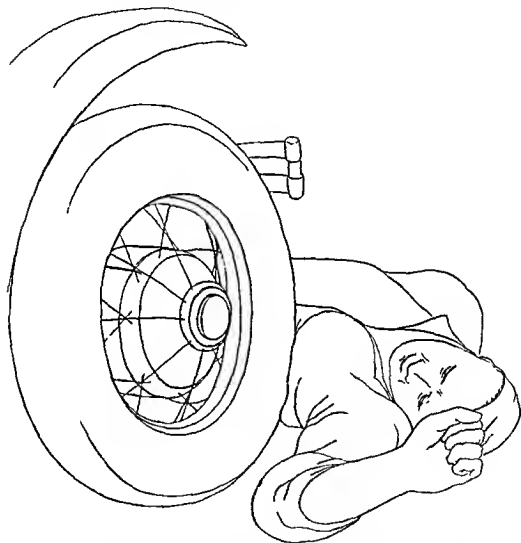


FIGURE 9 An injury of this type can produce circulatory shock, rupture of the diaphragm and contusion of the heart. The circulatory shock is due to cardiac contusion and not to the rupture of the diaphragm.

sudden severe compression One would expect that a trauma of this nature would be more destructive if it should be applied at the end of diastole or at the beginning of systole, when the heart is filled with blood. One would also expect this trauma to be more destructive if it should

be applied from the base of the heart toward the apex, so that the blood cannot escape as the heart is compressed

The heart can be ruptured by breaking open the friable myocardium. This can occur even though the heart is emptied of blood. The heart can be ruptured by softening of the bruised area. Analysis of the litera-

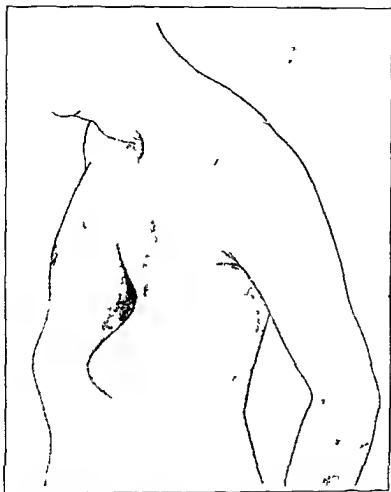


FIGURE 10 This patient was kicked by a colt over the precordium. The patient became a chronic cardiac invalid.

ture shows that if the patient survives the first nine hours after injury the chances of surviving the first week are better than his chances of surviving the second week. One would expect the greatest amount of softening of the injured myocardium to be present during the second week and this point should be given special consideration in the treatment of these cases so that such blowouts of the heart may be avoided.

Another mechanism by which the heart can be ruptured is by sudden distention with blood. This can occur when the blood is forcibly driven from the legs and abdomen as when the body is engulfed in a cave in accident (Fig 11). Spontaneous rupture of the right auricle has occurred.

Incidence of Cardiac Contusions: In 1935 Bright and Beck analyzed the literature on nonpenetrating injuries of the heart and found 152 instances of cardiac rupture, 11 instances of failure without rupture and



FIGURE 11 Cave in accident Rupture of right auricle

12 instances of recovery. In the recovery group the diagnosis was based upon clinical manifestations. According to this analysis, it appears that when the human heart received a contusion, death was the rule and recovery was the exception. According to experimental data the heart can withstand an enormous amount of contusive trauma and recover. In the experiments, recovery was the rule and death was the exception. We can conclude from these data that the group of human cases in which recovery took place was much smaller than it should have been. *The clinical diagnosis of cardiac contusion is made too infrequently. It is my belief that contusions of the heart are fairly common. I believe they are of commoner occurrence than the penetrating wounds of the heart.*

Symptoms and Diagnosis: Weakness coming on after the accident is the commonest symptom of cardiac contusion. When the contusion

is produced experimentally there is a fall in arterial pressure but as a rule the fall in pressure is of transient duration. In the less severe cases of contusion the weakness is momentary. The patient extricates himself from the wreck, sits down for a while and is then on his way. In cases of severe contusion the circulatory shock can be extreme. The patient may be unconscious, the arterial pressure low and the skin cold and clammy. Restlessness and air hunger may be present. Tachycardia is the rule but bradycardia is sometimes present. Hemorrhage in the region of the bundle of His produces heart block.

The heart sounds are distant and resemble the ticking of a watch. Auricular fibrillation if it appears is usually transient but it can be permanent and disabling. Pericardial discomfort or pain is almost always present. It may be in the epigastrium or it may radiate into either arm. Vomiting sometimes occurs. The pain as a rule occurs immediately after the accident but it can occur after a latent period. It can grow worse over a period of days or weeks following the accident. It varies from a discomfort or ache to a sharp anginal pain.

The electrocardiogram shows alterations from the normal. The QRS complex shows slurring and notching. Deep Q waves, large T waves, high take-off of T and inversion of T were frequently encountered in experimental studies. In our experiments those deviations from normal usually disappeared in the course of four to six weeks. The electrocardiographic changes that are due to hemorrhage disappear after the blood is absorbed. Those that are due to destruction of muscle are permanent.

The diagnosis of cardiac contusion not infrequently becomes a problem of patient *versus* insurance company. Some of these problems are extremely difficult to settle. For example, a man is thrown out of his seat in a train accident and strikes his chest against a seat. He dies a few hours later and coronary sclerosis is found at autopsy examination. A woman who never had signs or symptoms of heart trouble is thrown from the seat in a car accident. The lumbar muscles are bruised but she does not know whether or not she struck her chest. Auricular fibrillation develops immediately after the accident. Later an embolus lodges in a femoral artery and the leg must be amputated. Did this patient sustain an injury to the heart producing auricular fibrillation or did the injury accentuate a cardiac lesion that was present but had not manifested itself or was the injury entirely incidental?

Following is a brief summary of a case of cardiac contusion

A delivery man for a bakery 25 years of age ran his truck into an automobile and demolished the front end of his truck. His chest was thrown forward against the steering wheel. He transferred his load of bakery goods into another truck and proceeded with the delivery. He worked the following day and experienced some upper abdominal pain. On the second day following the accident he experienced weakness and shortness of breath. He continued to work but on the fourth day con-

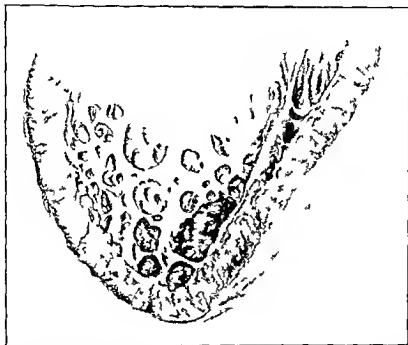


FIGURE 10 Steering wheel accident produced cardiac contusion mural thrombus pulmonary embolus hemoptysis and death. (This is a drawing of thrombus in the right ventricle.)

sulted a physician. At that time he had dyspnea on exertion, pain in the chest, and a pulse rate of 120 per minute. Slight discoloration of the skin was found over the left seventh costal cartilage. On the eighth day following the accident he worked 14 hours but with great difficulty. The next day he was unable to work. His symptoms were weakness, dyspnea, pain in the chest, and pain down the right arm. He again consulted his physician. He was in bed at home for seven days and in a hospital for ten days. He walked home and had to stop several times because of dyspnea and weakness. Blood-stained sputum appeared. The heart dilated and signs of failure appeared. He died 85 days after the accident. Mural thrombi were found in the right ventricle and in the left ventricle (Fig. 12). Pulmonary emboli were found and these most

probably originated from the mural thrombus in the right ventricle. The seventh costal cartilage was broken. The heart wall directly beneath this cartilage had the thrombus. The accident sustained by this patient was a steering wheel injury which produced myocardial contusion, cardiac weakness, dyspnea and pain, mural thrombi, pulmonary emboli, cardiac failure and death.

Treatment: The symptoms can be transient and recovery rapid. Weakness and tachycardia may require rest in bed. I have observed the ventricles go from a rapid ventricular tachycardia to ventricular fibrillation following contusive trauma. If quinidine can prevent the development of ventricular fibrillation its use is indicated. Oxygen is indicated in the presence of dyspnea and cyanosis. Morphine and other sedatives should be used to induce rest and quiet.

Softening of the bruised muscle takes place especially in the second week and there is a danger of rupture of the heart. Exertion is to be avoided. Straining at the stool, coughing, etc., are to be avoided. Surgical intervention is indicated if rupture occurs. It seems that operation might have been feasible in some of the patients in whom death occurred from rupture. In some of these instances, the bruised area was not so extensive but that sutures could have been placed to close the opening in ventricle or auricle. A graft of fascia lata or parietal pericardium can be placed upon the contusion to prevent rupture and the formation of an aneurysm of the heart. Up to the present time this operation has not been done on the human heart. We have repaired by suture rupture of the heart produced experimentally, and we have reinforced the heart wall by free grafts. Perhaps these procedures can be applied to the human heart. The opportunity to do this operation is fleeting, but there are instances in which there is sufficient time to do the operation.

HEMOPERICARDIUM

Hemorrhage into the pericardial cavity occurs in the following conditions: Penetrating wounds of the heart and intrapericardial segments of the great vessels, contusion of the heart without rupture of the heart, contusion of the heart with rupture, spontaneous rupture of an auricle or ventricle, rupture of a myocardial infarct, rupture of an aneurysm of a ventricle, rupture of the base of a sclerotic aorta, tumor of the heart, scurvy, the hemorrhagic diatheses, rheumatic fever.

The hemorrhage can occur rapidly or slowly. It can be constant until death occurs or it can stop. It can recur. If the bleeding is slow or intermittent a large quantity of fluid can be contained in the pericardial cavity because the pericardium stretches in response to the continued low grade pressure within.

The *clinical signs and symptoms* produced by an accumulation of blood or bloody fluid in the pericardial cavity vary with the rapidity of its formation. Usually the signs of acute cardiac compression are produced but slow and intermittent bleeding can produce the symptoms of chronic cardiac compression.

The *diagnosis* of hemopericardium is obvious in many instances. If the nature of the fluid is obscure removal of fluid by aspiration is carried out. The thin bloody exudates are treated by aspiration rather than by operation.

The proper *treatment* requires nice judgment. Repeated episodes of bleeding from the right auricle took place in a case reported by Clowe, Kellert and Gorham. There was no history of trauma in this patient. Exploration and suture of the auricle was indicated in this condition in much the same way as in a penetrating wound of the heart that emits blood. Munsell Moullin in a timely operation removed a blood clot from the pericardial cavity in a boy who received a nonpenetrating cardiac injury in a Rugby game. We should not be too conservative in performing operation for purposes of exploration. Sauerbruch operating for a condition that he thought was a mediastinal cyst opened into an aneurysm that came off the right ventricle. The thin walled sac could not be closed because the sutures tore out. He then inserted two fingers into the structure and plugged the communication with the ventricular cavity. Excision of the sac and closure of the ventricle were successfully accomplished.

PURULENT PERICARDITIS

Purulent pericarditis should be suspected in any patient who shows signs of either acute or chronic compression of the heart in the presence of infection. It can occur as a complication or as a sequel to pneumonia, osteomyelitis, empyema of the thorax, throat infections, cholecystitis, appendicitis, peritonitis, etc. The infection can be introduced through a penetrating wound in the chest. It can be introduced with a foreign body like a fish bone or a needle from the esophagus (Fig. 13). In some instances the infection is blood borne.

intermediate between the acute and chronic stages. It is acute in that the arterial circulation is markedly impaired and the veins are not enlarged. It is chronic in that the liver is enlarged and edema is present in the scrotum and ankles. Empyema of the left chest and subcutaneous abscesses developed. Improvement followed drainage. All wounds healed and the patient was discharged from the hospital October 26, 1935. The liver became smaller. The temperature was normal and there was no evidence of infection.

January 8, 1936, the child was readmitted to the hospital for study. He showed slight evidence of chronic compression of the heart. On the venous side of the circulation were the following manifestations of stasis—subcutaneous edema, ascites, pleural effusion, each of slight degree. Cyanosis, enlargement of the veins and enlargement of the liver were absent. On the arterial side was a systolic pressure of 85 mm of mercury and a diastolic pressure of 50 mm of mercury. The heart sounds were normal.

On June 11, 1936, the patient was readmitted for study. The arterial pressure was 78 mm of mercury systolic and 60 mm of mercury diastolic. The venous pressure was 15 cm of water. The liver was slightly enlarged. Slight edema of the ankles was present. The precordium was quiet. The cardiopericardial shadow was becoming smaller. The heart was becoming compressed by the contracture taking place in the scarified pericardium. The degree of compression became more marked during the next six months—a condition that anyone who is familiar with the chronic compression triad could recognize in a moment and recognize by inspection alone without any of the special tests (Fig. 14 A).

He had (1) a quiet heart as shown by inspection of the precordium, (2) increased pressure in the superior vena cava as shown by inspection of the enlarged veins in the neck and arms and cyanosis of the capillaries bed in the nails and (3) increased pressure in the inferior vena cava as shown by inspection of the swollen ankles and swollen scrotum and enlarged abdomen. All other manifestations were secondary to these three primary components of this disease triad. As a rule the heart is normal before it becomes compressed. Compression being an extrinsic disorder should not produce murmurs. The compressed heart is efficient although it is not adequate to meet the requirements of a normal intake and output. It does not waste energy. It undergoes atrophy of disuse. The x-rays showed a progressive diminution in the size of the pericardial shadow during the preceding year. The heart was not fixed in position. The electrocardiogram showed low voltage and slurring of Q R S complex. The diastolic systolic excursion was reduced (Fig. 4 A). The veins were dilated. Pulsus paradoxus was present. The pulse pressure was 20 to

80 mm of mercury. Ascites was present. The liver was enlarged. Subcutaneous edema of ankles and scrotum were present.

Operation December 3, 1936. The scar was two to three millimeters in thickness, intimately adherent to the heart. Sharp dissection was necessary to separate it from the heart. Separation was carried out over the anterior and lateral surfaces and the scar was excised. The heart dilated after this was done, indicating that the compression was corrected. The child made an excellent recovery. The cyanosis disappeared. The venous

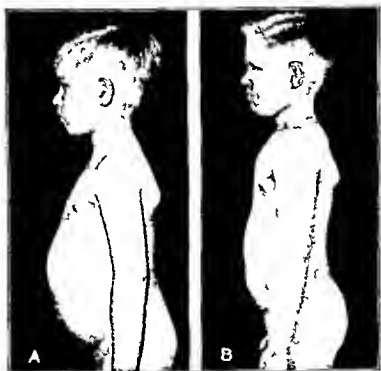


FIGURE 11. Compression of heart by scar. *A*, Before operation. *B*, After operation. A complete cure. See Fig. 4.

pressure measured 17 cm. Ascites and edema disappeared. The liver became smaller. The diastolic-systolic excursion of the heart improved and the pulse pressure increased. The child is active, attends school and is growing.

Pus forms rapidly or slowly. Usually it develops so rapidly that the pericardium does not have time to stretch as it does in the sterile effusions or in the tuberculous effusions. The clinical picture is that of acute cardiac compression but edema, ascites and enlargement of the liver can appear in a few days and the picture of chronic cardiac compression can develop.

As a rule the patient is acutely ill. The circulation is poor, the arterial pressure is low, the hands and feet are cold, clammy and cyanotic and

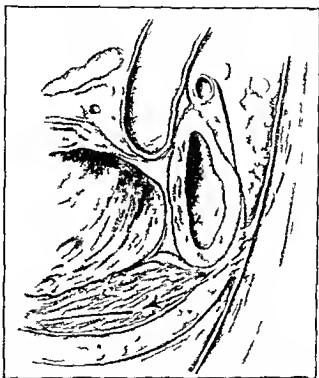


FIGURE 13 Fore gut body (needle) penetrates heart from esophagus

the patient is toxic from the infection. The presence of purulent pericarditis should be suspected in every patient who has an infection such as osteomyelitis or pneumonia and who is not doing so well as he should in consideration of the infected lesion. The pressure on the heart must be released and the pus must be evacuated if the patient's life is to be saved. This must be done as early as possible.

After the diagnosis of purulent fluid is confirmed by aspiration of pus, open incision and drainage are carried out. The operation should not be any more extensive than necessary. The anesthetic of choice is

novocain Inhalation anesthesia must be carefully given because the patient tolerates poorly any inhalation anesthetic drug. The left fifth or sixth costal cartilage is removed. The pericardium is opened and the margin of the pericardial incision is sutured to the skin. The pericardial cavity can be irrigated with warm physiologic solution of sodium chloride. Antiseptic chemicals, especially Dakin's solution, should never be used. The pericardium cannot tolerate antiseptic solutions. Rubber tubes and drainage materials should not be placed in the pericardial cavity because of the possibility of erosion of a vessel. Occasionally a pocket of pus forms but in my experience the cavity becomes obliterated without abscess formation and the wound heals.

A boy aged six years was admitted to the University Hospitals July 28, 1935, with fever, sore throat, labored respiration and substernal pain. His illness began six days before admission with sore throat and stiffness of the neck. The cervical lymph nodes on one side became enlarged. Two days later pain on breathing appeared beneath the sternum and respiration became shallow and labored. The temperature was elevated. The lungs were clear. Upon admission to the hospital the patient was acutely ill. He was dyspneic and cyanotic. The extremities were cold. The pharynx was slightly injected. The precordium was quiet and did not show any pulsation. The heart sounds were distant and could not be clearly distinguished. There were no murmurs. The area of cardiopericardial dullness was increased. The liver was tender and slightly enlarged. The pulse rate was 120 to 130 per minute. The pulse was thready and irregular. Respiration rate was 42 per minute. The systolic pressure was 86 mm. of mercury. The electrocardiogram showed slurring of QRS in all leads with deep S in Lead I. T was upright in all leads and the ST take off was elevated in all leads.

An aspirating needle was inserted into the pericardial cavity and 100 cc. of greenish yellow thin pus containing type four pneumococcus was removed. The circulation immediately improved after this fluid was withdrawn but the improvement was temporary. Aspiration was repeated on the following day with beneficial result but the improvement was again temporary. Operation was carried out. Light nitrous oxide anesthesia was used. The left fifth costal cartilage was removed. The internal mammary vessels were ligated above and below. The pericardium was incised. Fluid spurted about 20 cm. from the wound. Three hundred cubic centimeters of pus were removed. The heart was covered by fibrin. The pericardium was sutured to the skin. Marked improvement in the condition followed. The following quotation was taken from my operative note — This child represents a type of cardiac compression which is

intermediate between the acute and chronic stages. It is acute in that the arterial circulation is markedly impaired and the veins are not enlarged. It is chronic in that the liver is enlarged and edema is present in the scrotum and ankles. Empyema of the left chest and subcutaneous abscesses developed. Improvement followed drainage. All wounds healed and the patient was discharged from the hospital October 26, 1935. The liver became smaller. The temperature was normal and there was no evidence of infection.

January 8, 1936, the child was readmitted to the hospital for study. He showed slight evidence of chronic compression of the heart. On the venous side of the circulation were the following manifestations of stasis—subcutaneous edema, ascites, pleural effusion, each of slight degree. Cyanosis, enlargement of the veins and enlargement of the liver were absent. On the arterial side was a systolic pressure of 85 mm. of mercury and a diastolic pressure of 50 mm. of mercury. The heart sounds were normal.

On June 11, 1936, the patient was readmitted for study. The arterial pressure was 78 mm. of mercury systolic and 60 mm. of mercury diastolic. The venous pressure was 15 cm. of water. The liver was slightly enlarged. Slight edema of the ankles was present. The precordium was quiet. The cardiopericardial shadow was becoming smaller. The heart was becoming compressed by the contracture taking place in the scarified pericardium. The degree of compression became more marked during the next six months—a condition that anyone who is familiar with the chronic compression triad could recognize in a moment and recognize by inspection alone without any of the special tests (Fig. 14A).

He had (1) a quiet heart as shown by inspection of the precordium, (2) increased pressure in the superior vena cava as shown by inspection of the enlarged veins in the neck and arms and cyanosis of the capillary bed in the nails, and (3) increased pressure in the inferior vena cava as shown by inspection of the swollen ankles and swollen scrotum and enlarged abdomen. All other manifestations were secondary to these three primary components of this disease triad. As a rule, the heart is normal before it becomes compressed. Compression being an extrinsic disorder, should not produce murmurs. The compressed heart is efficient although it is not adequate to meet the requirements of a normal intake and output. It does not waste energy. It undergoes atrophy of disuse. The x-rays showed a progressive diminution in the size of the pericardial shadow during the preceding year. The heart was not fixed in position. The electrocardiogram showed low voltage and slurring of QRS complex. The diastolic systolic excursion was reduced (Fig. 14A). The veins were distended. Pulsus paradoxus was present. The pulse pressure was 20 to

80 mm of mercury. Ascites was present. The liver was enlarged. Subcutaneous edema of ankles and scrotum were present.

Operation December 3, 1936. The scar was two to three millimeters in thickness, intimately adherent to the heart. Sharp dissection was necessary to separate it from the heart. Separation was carried out over the anterior and lateral surfaces and the scar was excised. The heart dilated after this was done, indicating that the compression was corrected. The child made an excellent recovery. The cyanosis disappeared. The venous

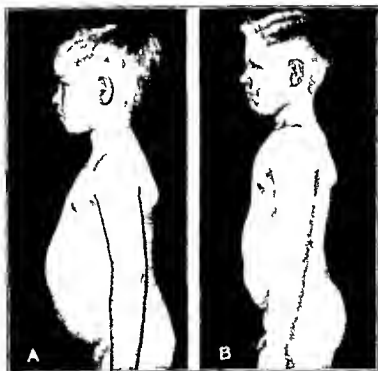


FIGURE 14. Compression of heart by scar. *A*, Before operation. *B*, After operation. A complete cure. See Figure 4.

pressure measured 17 cm. Ascites and edema disappeared. The liver became smaller. The diastolic systolic excursion of the heart improved and the pulse pressure increased. The child is active, attends school and is growing.

CARDIAC COMPRESSION DUE TO SCARS

Etiology. The compression scars are always extrinsic in origin. They never develop as a sequel or complication of an intrinsic lesion. They never originate from rheumatic heart disease. The infection finds entrance into the pericardium from the pharynx, lungs, pleura or mediastinum. However, Dakin's solution and other chemical irritants applied

to the normal pericardium of animals result in scars that later undergo contracture and produce compression of the heart. In my series of operated cases seven showed evidence of tuberculosis in the scars and 30 did not show evidence of tuberculosis in the scar removed at operation. Two of this group of 30 patients however had tuberculosis elsewhere without showing tubercles in the scar.

Diagnosis. The author's triad makes the diagnosis of chronic cardiac compression simple and infallible (Fig. 3). Usually the diagnosis can be made by inspection alone. The ascites is apparent, the distention of the venous system is apparent and the quiet precordium is readily observed. Our understanding of cardiac compression has been greatly simplified by placing proper emphasis upon the compression and by eliminating the old terminology of adhesive pericarditis, Pick's disease, mediastinopericarditis and constrictive pericarditis together with the implication that the heart undergoes dilatation, hypertrophy and failure because it pulls upon adhesions. That the compressed heart is entirely free from these assumed disturbances even though adhesions are everywhere present has been demonstrated beyond any reasonable doubt.

Differential diagnosis as a rule is not a problem. Obstructions elsewhere at the tricuspid valve, at the pulmonic valve, at the pulmonary artery, at the mitral valve, at the aortic valve and the aorta have characteristics that make the localization of the obstruction at these sites possible. I have seen several patients with the obstruction in the pulmonary bed due to chronic pulmonary infection and fibrosis with narrowing of the smaller vessels in the pulmonary bed. These patients showed the signs of stasis in each ventricle with ascites and cyanosis but the heart made a normal diastolic-systolic excursion. In the absence of a quiet heart the diagnosis of compression was not made and the fibrotic appearance of the lungs placed the obstruction in the lungs.

Compression of the heart due to scar is to be differentiated from compression due to other agents such as fluid in the pericardial cavity, blood exudate, transudate or a neoplasm. The size and contour of the x-ray shadow helps here. If fluid is suspected aspiration might be carried out before operation is done. In several of my patients the compression was due to a combination of fluid and scar.

The compressed heart is always small. The small atrophic condition of the heart may or may not be suggested by the x-ray shadow. Scars vary

from one to about ten millimeters in thickness and a thick scar can give the atrophic heart the appearance of being either normal or enlarged.

Operation for Removal of Compression Scars: The patient should be free of fever before resection of the compression scar is carried out. Patients with tuberculous scars may require months of medical treatment before the fever subsides. In some cases fever will not subside even after the patient has been placed on a medical regimen. The patient may become progressively worse so that operation must be done in the presence of infection. Whenever possible it is advisable to wait until the infection becomes quiescent. Dehydration should be carried out before operation. Repeated tapping of chest and abdomen may be necessary. Diuretics are used.

Quinidine is given to reduce the irritability of the heart. A test dose of three grains is given in the afternoon before operation, and if the patient shows no untoward reaction five grains are given that night and five grains the next morning before operation. Glucose and orange juice are given to the patient several hours before operation. Atropine and a small quantity of morphine are given as preanesthetic drugs. Sedatives are used with precaution. Avertin should not be used. It can paralyze the respiratory center in these conditions.

I prefer light anesthesia and use nitrous oxide, oxygen and ether. Deep anesthesia is contraindicated. I use a semirecumbent position, the patient reclining at an angle of 45 degrees. Respiration is better in this position than in the horizontal position. An intratracheal tube is not used. Positive pressure insufflation should be available, but care should be taken not to inflate the lungs forcibly. If the lungs are forcibly inflated, the pulmonary resistance is increased and an added burden is placed upon the right ventricle—a burden which can result in right ventricular dilatation and ventricular fibrillation.

The incision is usually made on the left of the sternum. In exceptional cases, the incision is made on the right side of the sternum. These exceptional cases have compression of the right side of the heart with the left side free. I use a transverse incision over the fourth interspace or below the left breast. The pectoral muscle is exposed and is cut across its fibers to expose the left third, fourth and fifth costal cartilages. These are removed. The internal mammary artery and vein are ligated high in the wound. The intercostal bundles and triangularis sterni muscle are

cut and the mediastinum is entered. The pleural sinus is dissected down to the left phrenic nerve. The scar is incised to its proper depth from apex well up over the base where the pericardium comes away from the great vessels. It is then separated from the heart and I carry out this separation on the left side before the right side is done. Schmieden states that the left ventricle should be decompressed before the right ventricle is decompressed.

In some cases the separation of scar from the heart can be done with blunt dissection. In other cases sharp dissection is necessary. The separation should be as extensive as possible. If the separation posteriorly can be done safely by the finger this is done but care must be taken not to tear the myocardium with the finger. Otherwise the heart is left adherent posteriorly. The right pleural sinus is dissected laterally. In doing this the heart is rotated and rest periods are given frequently. The left pleural sinus is widely opened to establish internal drainage *i. e.* from the mediastinum into the left pleural cavity. The scar is excised as widely as possible. The intercostal bundles are sutured. The pectoral muscle is sutured. Air is removed from the pleural cavity by suction and the wound is closed.

The coronary vessels are to be avoided. Traction upon the scar can pull a coronary artery from its bed and in dissecting the scar from the heart muscle it is advisable to cut well towards the scar. Pressure with a finger on a coronary artery can occlude the artery which in turn can produce ventricular fibrillation. The ventricular muscle can be torn by the finger in dissecting the scar by blunt dissection. The auricular wall can be easily torn. Sometimes the heart reacts from surface stimuli and two per cent procaine can make the heart less irritable. It can be applied to the surface as well as injected intravenously. At the same time however procaine reduces the tone of the heart muscle and it should be used with caution. Rotation and angulation of the heart are poorly tolerated. Touching the heart produces extrasystoles. Local pressure upon auricles and right ventricle reduces the capacity of these chambers. Rest periods are beneficial.

Postoperative Care. The patient is placed in an oxygen tent immediately after operation. Sedatives are given as indicated. Fluids are not given by the intravenous method. The compressed heart always dilates after the compression scar has been removed. In selected cases it might

be advisable to reduce the venous pressure and the dilatation by blood-letting. This is recommended only in those patients with a high degree of compression and in whom the heart has become weak and atrophic. Improvement in the circulation is noticeable as soon as the scar is removed. As a rule, the heart action is better immediately after resection than it is after the first few hours. In cases of severe compression the atrophic heart struggles with its additional work for days, weeks or months before the waterlogging disappears. The heart must get stronger and the atrophy must disappear before the heart can perform its full quota of work. Some of my patients showed an early diuresis after operation, taking place in 48 hours. In some patient all excess fluid was lost within a week or two. In other patients edema and ascites recurred after a temporary diuresis had taken place. As a rule, the patient is ambulatory in from four to six weeks.

Results Obtained After Resection of Compression Scars: Analysis of literature and personal communications shows that 177 patients with compression scars were operated upon by 51 surgeons. Of these Beck had 37 (1939); Schmieden, 22 (1937); Blalock, 14 (1939), Churchill 12 (1936); Tengwall, 7 (1938); Heuer, 7 (1939), L. Rehn, 1 (1920), De Quervain, 4 (1934); Sauerbruch, 4 (1925); Boichardt, 4 (1938), Lâwen, 3 (1928); Volker, 3 (1933); Whittemore, 3 (1935), Budisavljevic, 3 (1931). The number of patients listed as cured was 74, or 41.8 per cent; as improved, 41, or 23.2 per cent; as not improved, one, or 0.5 per cent; as not classified, four, or 2.3 per cent, and as died, 57, or 32.2 per cent.

It should be emphasized that the great majority of patients with compression scars can be completely cured by operation. We should expect a cure to take place in every patient who has an extrinsic scar and who does not have active tuberculosis elsewhere. In a small proportion of patients the atrophy of the heart muscle is so extensive that the heart may or may not be able to make the initial adjustment to the increased work placed upon it.

Of my series of 37 patients operated upon, 25 are completely free of ascites and edema and can be classified as cured, three additional patients have been operated upon recently and probably will be cured, two patients are improved and seven died. Of the two patients improved one had invasion of the myocardium by scar and one had reformation of

calcium deposits around and in the myocardium. Of the seven deaths three had active tuberculosis in the pleurae and mediastinum, one had an epicardial scar plus bloody fluid and died of infection, two died of heart failure from atrophy of the heart and one of ventricular fibrillation during operation. At the present time we are prepared to defibrillate the ventricles at the time of operation.

LIGATION OF THE PATENT DUCTUS ARTERIOSUS

In 1907 John Munro suggested that the ductus arteriosus might be ligated if it remained patent. There appears to be no record of an attempt

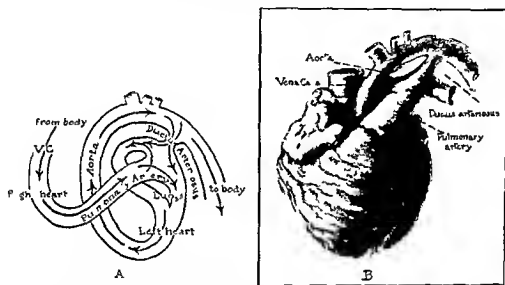


FIGURE 15 A Diagram of circulation showing the short circuit of blood through the patent ductus arteriosus. B Heart of a child three days old illustrating patent ductus arteriosus (Nelson Loose Leaf Surgery)

to perform the operation until 1937 when J. W. Strieder recorded an unsuccessful attempt to ligate the structure in a patient who had bacterial endocarditis. The operation has been under consideration by several American surgeons and recently John Hubbard selected the first patient upon whom the ductus was successfully ligated by Robert Gross. Within the last two years Gross has done nine successful operations. These admirable accomplishments by Gross have placed the patent ductus arteriosus in the domain of surgery. Dolley and his associates have operated upon 13 patients. Tourroff recently cured a patient with subacute bacterial endocarditis by ligation of the patent ductus arteriosus. Additional cases have been done by Gurd, Holman, Bigger and Brunn.

Figure 15 illustrates the shunt in the circulation produced by this communication. In this condition blood flows from the aorta where the pressure is relatively high into the pulmonary artery where the pressure is lower. A part of the oxygenated blood in the aorta is returned to the lungs and a short circuit is thus set up. This shunting of the blood stream is followed by certain complications. In the first place the heart has increased work placed upon it. The left ventricle dilates and undergoes hypertrophy in a manner similar to that seen when a fistula connects any large artery and vein as in the femoral region or in the neck or axilla. The right ventricle also works against an increased resistance in the pulmonary bed. Endocarditis may develop at any time in a patient with a patent ductus arteriosus. Growth and nutrition can be affected by the condition and it would appear that the wall of the ductus is sometimes thin and may rupture.

Selection of Patients. In deciding whether a patient should be operated upon we must consider the risk of the operation and also the risk without the operation. Experience with the operation is so limited that the first question cannot be answered. Doctor Gross had nine successful operations and one death. Doctor Stueder had one failure. We had a patient upon whom we considered doing the operation but the patient died of bacterial endocarditis. In this patient the anatomy was such that closure of the fistula seemed to be an impossibility. Granted that ligation or closure is an impossibility in an unknown proportion of the cases we can say that exploration to determine operability should carry a negligible risk.

What risk does a patient take without operation? We know a patient can go along without any serious trouble from the patent ductus. It is also known that in some children the closure is delayed but does progress slowly to completion. The studies by Abbott give us some information. In a study of 1000 congenital defects she found 92 uncomplicated instances of patent ductus arteriosus. How long these 92 patients lived and from what they died is of importance in determining the risk that a patient takes with a patent ductus arteriosus. The oldest was 66 years, the youngest two weeks and the average was 24 years. Quoting Abbott under proper precautions (removal of foci of infection etc.) the subjects of patent ductus may and do live on in full exercise of their activities into advanced middle age. To me this statement is more optimistic

than the figures would indicate. The causes of death in this group of 92 patients were listed as follows: Sudden 16, heart failure 24, bronchopneumonia 3, cerebral disease 3, bacterial endocarditis or endarteritis 21, other causes 16 (this makes a total of 83).

It would appear then that the cause of death was related to the patent ductus in about 80 per cent of the patients and that it was not related to the cause of death in only 20 per cent of the cases. If these proportions are only approximately correct, it would appear that operation is indicated in the majority of patients with patent ductus arteriosus. It is quite impossible to foretell in any patient, regardless of how well the patient is at any given time, whether he will become one of the 20 per cent who will not die from the patent ductus and its associated complications. The operation has two purposes—first, exploration and second, ligation or closure of the communication if feasible. The subject deserves careful consideration by the internist and by the surgeon.

The Operative Procedure. The operation as performed by Gross utilizes a transverse incision such as I advocate for the removal of compression scars. The approach through the chest must be at the level of the second or third costal cartilage. In female patients I would suggest that the transverse incision be placed beneath the left breast where it would not be seen. The second and third costal cartilages can be removed or cut across and retracted. Gross opens the left pleural cavity for exposure of the phrenic nerve and incises the pleura posterior to the nerve. The aortic arch and the pulmonary artery are exposed and the thrill is located. Pressure on the ductus by the finger obliterates the thrill.

Gross advises isolation of the recurrent nerve to prevent injury and to locate the communication. The ductus is dissected free and an aneurysm needle carrying the ligature material is placed around it. Trial closure of the communication is carried out to determine the reaction of the heart. If the communication is compensatory to another unsuspected abnormality that is present, the circulation might become impaired to a greater extent when the ductus is closed than when it is open.

If the heart reacts satisfactorily, permanent ligation is done. Silk undoubtedly is the ligature of choice. It should be coarse. The ligature should not be placed excessively tight because it seems that erosion of the vessel is less likely to occur if the ligature just obliterates the lumen

of the vessel (Halsted) Double ligation of the vessel was carried out by Gross in the last two patients I would condemn the injection of a few drops of some chemical so called sclerosing solution between the two ligatures as suggested but not used by Gross An artery carrying blood under pressure should never be subjected to the chemical necrosis of such solutions The closure of the wound is as usual

Results After Ligation In September 1939 Gross reported the results in his first four patients All were living The thrill disappeared in each patient The diastolic pressure rose to normal levels in each patient after operation—a rise of some 30 mm of mercury The systolic pressure was normal before as well as after operation Cardiac activity was reduced to normal by the operation and the heart appeared smaller by x rays in two patients One gained weight and both returned to school

Some interesting studies in blood flow were made in these patients These are quoted from Gross as follows In Cases 3 and 4 samples of blood (for oxygen content) were taken during operation from the aorta the ductus the main pulmonary artery and the left pulmonary before and after ligation of the ductus After determining the patient's oxygen consumption it was then possible to calculate the volume of blood flowing to the periphery through the ductus and through the right and left sides of the heart These studies are reported more fully elsewhere but a few of the findings are listed here In Case 3 the peripheral blood flow was 4.86 liters per minute while the ductus was still open and was increased to 6.12 liters per minute after the ductus was ligated In Case 4 the peripheral blood flow was 5.8 liters per minute while the ductus was open Concurrent with this peripheral flow 18.8 liters of blood per minute passed through the ductus making a total of 24.6 liters which the left ventricle had to pump per minute in order to maintain the peripheral flow at a normal level Following ligation of the ductus the left ventricular output was 5.08 liters per minute and this entire amount was of course distributed to the periphery In short this heart was performing more than four times as much work as was necessary while the ductus was open It is at once evident that ligation of the ductus greatly increases the cardiac efficiency the increase in efficiency being dependent upon the size of the ductus which is obliterated (The above figures all represent conditions with the patients under cyclo

propane anesthesia and while the figures are somewhat higher than in the unanesthetized individual the general relationships are still true)

More recently Gross has reported on a total of ten patients nine of whom went through the operation successfully and have been greatly improved by the operation. There was one death from hemorrhage. Equally good results were obtained by Dolley and his associates in a series of 13 patients. Touroff operated upon four patients with bacteremia. In two of these the ductus arteriosus was thin and friable, and fatal hemorrhage occurred during operation. Successful ligation was carried out in the other two patients in one of whom the blood stream has become free of infection at the time of writing 17 weeks after operation. The other continues to have blood stream infection. Gurd's case presented friable structures which tore and which produced a fatal hemorrhage at operation. Biggers's case was successful in every way. One of Holman's patients still has a murmur.

THE PRODUCTION OF A COLLATERAL BLOOD SUPPLY TO THE HEART

Experimental In February, 1932, my associates and I began an experimental study of vascular anastomoses between the coronary arterial system and the vessels of grafts placed upon the heart. The tissues available for grafting upon the heart consist of parietal pericardium, mediastinal fat, skeletal muscle from the chest wall and various structures such as omentum, spleen, etc. brought up through an opening in the diaphragm. The epicardium was removed to establish satisfactory contact between graft and coronary vessels. Occlusion of the major coronary arteries was produced in various ways. In the early experiments silver bands were placed upon the arteries and these were squeezed together at successive operations. Later special clamps were devised to produce occlusion of a coronary artery and at the present time my assistant Dr. K. R. Phelps has devised a clamp that brings about occlusion of an artery by means of osmotic pressure. This clamp should be of considerable value to the experimental studies.

Briefly stated, the experimental studies demonstrated two major points. One consisted of the demonstration of vascular channels between graft and heart. In some experiments these anastomoses appeared to be large enough to carry considerable blood. We do not know how much

blood these anastomoses carried and indeed we cannot be certain concerning the direction of flow, whether it is into or away from the heart. The other point brought out by the experimental study concerns the distribution of blood in the myocardium.

Under normal conditions each of the major coronary arteries can be considered practically as an end artery. If the descending ramus of the left coronary artery is divided, only a few drops of blood per minute will flow from the distal end of the artery. These few drops of blood come from anastomoses with the circumflex and right coronary arteries and they are of little or no significance for carrying blood. However, if the descending ramus of the left coronary artery is occluded gradually, these intercoronary communications become important channels for carrying blood. In the presence of coronary sclerosis they are of great importance. Indeed, the preservation of the heart frequently depends upon intercoronary communications. The degree to which these vessels open up is variable and without doubt this variability determines at least in part whether a good or a poor adjustment is made to coronary closure.

We are of the opinion that the intercoronary communications can be influenced by inflammatory reactions on the surface of the heart. In our patients with coronary disease upon whom we operated, removing the epicardium and placing grafts upon the myocardium, clinical improvement was frequently noted within a few days after operation. The improvement could not be explained on the basis of extracoronary channels because it was too early for these to develop. We can put forth the supposition that the reaction following operation resulted in opening up intercoronary communications.

Vascularized Grafts for Coronary Artery Sclerosis: Thirty patients with coronary artery sclerosis were selected by Dr. Harold Feil and operated upon by me. The selection of the patients is of no importance to us at the present stage of development of this work. The operative technic is of little or no importance to us here. The mortality is of no significance at the present stage of development. The matter of importance is whether vascular communications numerous enough and large enough to carry a significant quantity of blood can be produced by any operative method on any patient. The late Laurence O'Shaughnessy operated upon patients using omentum for the graft, and Lockwood has used pectoral muscle, mediastinal fat and parietal pericardium.

Results of the Beck Operation: Various clinical measurements were made before and after operation. It appeared that the results of the operation were beneficial. In some patients the improvement was slight or absent but in others it was definite with reduction in pain and an increase in activity. More important information concerning the result of the operation will come from a study of the heart and grafts after the patient dies. So far we have had three specimens for study. One of these was from a patient who had a good clinical result. When the coronary arteries were injected with a solution of barium, the solution slowly dripped from the grafts and a number of anastomoses were found between heart and grafts. However, we desire to demonstrate better anastomoses before we can accept the operation as the procedure to be done for coronary artery sclerosis.

Vascular Anastomoses Produced by Chemical Agents: Recently Heinbecker introduced chemical agents into the pericardial cavity for the purpose of producing an inflammatory reaction between heart and parietal pericardium. He made injection studies and demonstrated anastomoses between pericardium and heart. He reported favorably concerning the results of his experiments and suggested application of this method to patients with coronary sclerosis.

Ligation of Coronary Veins for Coronary Sclerosis: There is clinical and experimental evidence to support the idea that when a major artery is ligated the corresponding vein also should be ligated. For example, if the femoral artery is severed so that it must be ligated, the surgeon should ligate the femoral vein also. This practice was adopted in the last world war.

Gross, Blum and Silverman carried out experiments on the coronary vessels to determine the effect of ligation of the coronary sinus. In these experiments the coronary sinus was occluded and then the descending ramus of the left coronary artery was occluded. These authors claimed that the mortality was not altered by the ligation of the sinus but the infarct was definitely smaller after sinus ligation. These authors hoped to apply this procedure of sinus ligation to the human heart in order to increase the vascular tree.

Gregg and Dewald carried out physiological studies on this subject and concluded that venous sinus ligation had little or nothing to recommend it. Fauteux of Montreal has done some experiments with favorable

results and recently ligated the magna cordis vein in a patient with coronary artery disease. Dr A. E. Miko and I have carried out over 100 experiments in which the vein and artery were ligated and we found that the ligation of vein has a slightly beneficial effect in reducing mortality and a questionable effect in reducing the size of the infarct. Whatever beneficial effect is produced by vein ligation in the heart is not very great. We are doubtful concerning the value of applying coronary vein ligation in the treatment of coronary artery sclerosis.

RESUSCITATION OF HEART FROM STANDSTILL AND FROM VENTRICULAR FIBRILLATION

When the pumping action of the heart ceases and the arterial pressure disappears the ventricles either come to a complete standstill or go into fibrillary twitchings before every vestige of movement leaves the organ. Either ventricular standstill or ventricular fibrillation is found in the heart when death overtakes the body. Restoration of the heartbeat has been accomplished with the heart in standstill but with two exceptions restoration of the coordinated beat has not been possible with the ventricles fibrillating.

A method is now available to defibrillate the ventricles. I have applied it successfully to two patients and these two experiences are perhaps the *first of their kind to be recorded*. Restoration of the heartbeat is possible only in patients who possess a good heart who are not the victims of disease and who die suddenly and unexpectedly in the operating room. The tragedy occurs in the operating room where the equipment for immediate action is available. If it occurs outside the operating room success is scarcely possible. These requirements reduce the possibilities *to about two to four patients a year for any large hospital*.

First Stage in Resuscitation This stage concerns the preservation of the brain and nervous system. The brain and nervous system remain viable from three to five minutes after the circulation ceases. If oxygen is not gotten to the brain within this brief period of time nervous system responses are lost and eventually the heartbeat after having been restored successfully, is also lost. Oxygenation is carried out by the anesthetist and by the surgeon who are with the patient when the circulation stops.

The anesthetist must deliver air or oxygen into the lungs. This is done most effectively by a special mechanical respirator which should be available in the operating room. The Drinker apparatus is not satisfac-

tory for this purpose. At the same time the oxygenated blood must be made to move to the brain. This is accomplished by the surgeon cutting through the fourth left interspace, opening the pericardium and massaging the heart. The blood pressure can be raised to 60 mm. of mercury by manual massage of the heart.

Second Stage in Resuscitation This stage concerns the restoration of the coordinated heartbeat. The heartbeat can be restored at almost any time provided the first stage is properly conducted. We have revived dogs' hearts after the lapse of an hour or even longer. Revival from standstill requires no special training. Frequently the heart starts up from the massage. Sometimes one or two cubic centimeters of epinephrine diluted in saline are necessary. It can be injected into the cavity of the *right ventricle*.

Defibrillation of the ventricles requires special training. The heart is well oxygenated so that it has a pink color. Two cubic centimeters of five per cent procaine are injected into the cavity of the right ventricle. Massage carries the drug into the coronary bed. Two electrodes of large size are placed on the heart and an alternating current of 15 amperes is sent through the heart. The fibrillation ceases with the shock and the heart is in standstill. Sometimes it starts beating from standstill, but if the heart muscle has lost its irritability and tonicity it remains motionless. Epinephrine or calcium chloride will restore these properties. The coordinated beat will return.

OPERATIONS ON CARDIAC VALVES

Considerable work has been done on the surgery of cardiac valves. Stenosis of the mitral valve, stenosis of the pulmonic valve and stenosis of the aortic valve have been operated upon for the purpose of decreasing the degree of stenosis even though a leak is thereby produced. Ten attempts on the mitral valve were carried out—seven by Cutler, one by Allen and Graham, one by Souttar and one by Pribram. Doyen inserted a knife into the right ventricle for the purpose of cutting a stenosis of the pulmonary valve. The patient died a few hours after the operation and at necropsy there was found a congenital narrowing of the conus arteriosus and perforation of the interventricular septum.

Griffin tried to dilate a stenotic aortic valve by inserting a finger through the invaginated wall of the aorta. Special instruments have been

devised to cut stenotic valves Attempts have been made to produce stenosis of the mitral valves experimentally Physiologic studies have been carried out to determine whether the circulation was improved by operation I shall not attempt to present the data on the stenotic mitral valve My belief is that little of practical benefit has come out of the work None of the operations have been established as acceptable procedures and the experimental work does not give any strong support for the operation Technically, any of the operations are feasible A mitral valve or any valve can be cut in so far as the procedure itself is concerned, but the changes in the circulation thereby produced are not definitely beneficial

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CHAPTER XXXVIII

RELIEF OF PAIN IN ANGINA PECTORIS BY PARAVERTEBRAL SYMPATHETIC BLOCK WITH ALCOHOL

By FRANCIS C. GRANT, M.D.

The problem of the relief of the pain of angina pectoris has for a long time engaged the attention of the medical profession. However, the surgeon was not involved in its solution until Jonnesco,¹ basing his surgical procedure upon the experiments of Francois Franck,² sectioned the stellate ganglia and cervical sympathetic chain bilaterally in the neck and reported that the pain was completely relieved. But the inability of other surgeons to confirm these findings resulted in much discussion and research upon the sensory pathways leading from the heart.

ANATOMY AND PHYSIOLOGY

The sympathetic nervous system carries sensory impulses from and motor impulses to the heart. Intensive research has been performed to determine precisely what components of the thoracicocervical sympathetic system contain the sensory afferent fibers so that interruption of the minimal number of pain pathways produced the maximum amount of relief of the angina. A short review of the more recently acquired knowledge concerning the anatomy and physiology of the sensory pathways from the heart is necessary.

The presence of typical somatic afferent pathways in the sympathetic cardiac nerves seems clearly proven. Rauson and Billingsley³ and Stohr⁴ have described the histology of these fibers. Heinbecker⁵ has confirmed these findings and shown further by the use of the cathode ray oscillograph that their conduction properties coincide exactly with those of the afferent fibers in the ordinary sensory nerves. In fact, in the strict sense these fibers are not of autonomic origin but are somatic fibers caught up in the sympathetic chain to carry afferent impulses from the heart to the sensory pathways in the spinal cord.

Stohr⁴ has demonstrated sensory nerve endings in the heart muscle endocardium and epicardium and in the adventitia of the coronary artery identical with those found in the heart and aorta. The sensory pathways from these endings pass along the periarterial plexus of the coronary arteries to the superficial and deep cardiac plexuses reaching the cervical ganglia of the sympathetic chain over the middle and inferior cardiac nerves. Since white rami connecting the cervical sympathetic chain and the spinal cord are lacking the vast majority of these sensory fibers must pass down the chain to the upper thoracic ganglia finally reaching their cells in the spinal ganglia through the white rami communicantes of the first thoracic and upper four or five intercostal nerves. The presence of these cervical cardiac nerves is well established. However Brücke⁶ and Ionesco and Enchescu⁷ have demonstrated the presence of thoracic cardiac nerves running directly across the posterior mediastinum to the upper four or five thoracic sympathetic ganglia. Somatic afferent fibers are present in all these nerves. Apparently therefore the upper four or five thoracic sympathetic ganglia receive all the sensory pathways passing from the heart towards the spinal cord.

BLOCKING OF SENSORY PATHWAYS

The problem now arises as to the evidence at hand concerning the safest and most effective way in which these sensory pathways can be blocked to cut off pain impulses from the heart. Sutton and Luth⁸ showed by temporarily constricting the descending branch of the left coronary artery in dogs that the characteristic signs of cardiac pain could be produced. Relief of the constriction resulted in rapid disappearance of the pain. Using this method White, Atkins and Garrey⁹ have shown that the cardiac pain thus produced could only be prevented from reaching the brain by bilateral excision of the stellate and the upper four thoracic ganglia or by resection of the upper five pairs of thoracic posterior roots. These results confirmed the earlier work of Spiegel.¹⁰

It is not our province to discuss here the surgical procedures used to relieve pain in angina. Resection of the upper four or five thoracic sympathetic ganglia, of the upper four or five thoracic posterior roots, stellate ganglionectomy, complete thyroidectomy or the attempt to develop a collateral circulation by the production of a new blood supply to the heart by grafting tissues into the myocardium are all major surgical procedures. To subject a patient whose cardiac muscle is already weakened

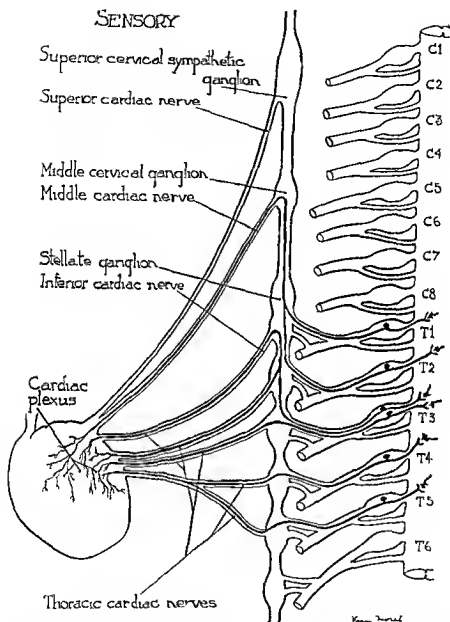


FIGURE 1 Diagrammatic representation of the cardiosensory pathways. These are true somatic afferent nerves; the ganglia of which lie in the posterior spinal root ganglia. No sensory fibers pass through the superior cervical sympathetic ganglion. Note that all sensory fibers from the heart pass through the upper five thoracic sympathetic ganglia and enter the cord through the corresponding posterior spinal roots. (Ochsner and DeBakey Surgery)

by a reduction in its blood supply to the added strain of a severe operation demands the most careful consideration.

Mindl¹¹ Brinn¹² and Swetlow¹³ have showed that a paravertebral block of the upper thoracic ganglia with alcohol would relieve the pain in angina pectoris. Mixter and White¹⁴ White¹⁵ Levy and Moore¹⁶ and Morav¹⁷ have confirmed these observations. Ochsner and DeBakey¹⁸ have recently reviewed the literature and tabulated the results in 68 cases in which this procedure has been carried out. In this series alcohol injection produced complete or partial relief in 80.9 per cent, failed to relieve pain in 17.6 per cent and resulted in one death, a mortality rate of 1.5 per cent.

The indication for paravertebral block is intolerable pain from severe cardiac disease. Less acute pain from a less threatening heart lesion might conceivably be subjected to one of the three surgical measures for its relief. Since these patients are on the verge of catastrophe the relatives should be warned that even alcohol block may result fatally. General anesthesia cannot be used for it masks evidence that the needles have been accurately placed. Careful preinjection medication is necessary to prevent psychic shock and dangerous distress during the procedure itself. Sufficient barbiturates to insure a drowsy patient at the time of injection are indicated.

TECHNIC

The instruments required are six rustless steel flexible lumbar puncture needles 10 cm. long. Bits of rubber tubing for depth markers and a metal centimeter rule should be included. A 10 cc. syringe which fits the needles closely and has a smooth action plunger should be used. Hypodermic needles, one per cent and two per cent procaine hydrochloride without epinephrine, 50 cc. (1 $\frac{2}{4}$ ounce) of absolute ethyl alcohol (C. P.), five per cent iodine and acetone to sterilize and mark the points of injection complete the outfit.

According to White¹⁹ the proper procedure for paravertebral injection is as follows. His technic is based upon that described by Labat.²⁰ The patient should be placed on his side on the edge of the bed with the knees drawn up and the head flexed forward. The head should be supported by a pillow so that the cervical spine is held straight. The hands should be uncovered and made easy of access so that their comparative warmth and dryness may be determined. It is preferable to

perform the injection with the patient in bed for any movement should be avoided for an hour following this procedure to permit the alcohol to become fixed in the tissues. Any lateral curvature of the cervical spine

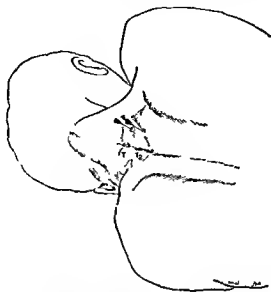


FIGURE 2 Paravertebral injection of thoracic sympathetic ganglia 1 Bony landmarks for inserting needles (White: *The Autonomic Nervous System* The Macmillan Co)

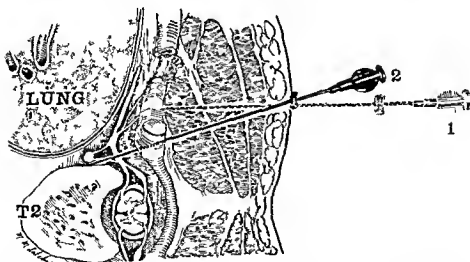


FIGURE 3 Paravertebral injection of thoracic sympathetic ganglia 1 and 2 Method of inserting needles (White: *The Autonomic Nervous System* The Macmillan Co)

which may change the anatomic relationships of structures to be injected is to be avoided. Furthermore, no one should attempt this technique without ample experience upon cadavers. The dissecting or autopsy room

is the place to learn this procedure before any attempt is made to apply it to a patient

The bony landmarks for paravertebral injection are the spinous processes. Due to their imbrication like the shingles on a roof the tip of each marks the level of the transverse process and the posterior angle of the rib next below. Thus the highest prominent vertebral spine the seventh cervical marks the level of the first rib. This relationship holds over the entire length of the thoracic vertebrae. In thin individuals it is a very simple matter to locate the spines but in the stocky type which so often goes with angina pectoris this may be a difficult matter. The points of injection are marked 3 to 4 cm lateral to the spinous processes. Following the use of tincture of iodine acriflavine applied with a fine cotton applicator is an excellent marking medium the two substances combine to form a jet black sterile mark.

Needles 8 to 10 cm long are inserted at the points so marked and pushed inwards perpendicular to the surface of the back. At a depth of 2 to 5 cm the needles should touch the transverse process or the rib. It is a great help to have on each needle a depth marker consisting of a short length of small bore rubber tubing. The lower borders of the ribs are located and the depth markers pulled out to a distance of 3 cm from the skin. The needles are then inclined slightly in a caudal direction and thrust down beneath the ribs at an angle of approximately 20 degrees towards the midline. Under these circumstances bone is usually felt again at a depth of 3 cm beneath the ribs evidence that the needle is in contact with the lateral aspect of the vertebra or the head of the corresponding rib. The sympathetic trunk lies at this depth running along the anterolateral aspect of the vertebra and looping over the heads of the ribs. Novocain injected in this region will diffuse freely through the retropleural areolar tissue infiltrating the spinal nerves the communicant sympathetic trunk and the ganglionated chain. The bony landmarks and the method of injection vary very little over the whole length of the dorsal spine.

In performing these injections the needle should never be attached to the syringe. Care should be taken that the tip of a needle does not lie within the pleural cavity in a blood vessel or in an abnormal outward prolongation of the subarachnoid space. With the needle touching bone it is almost impossible for its tip to be in the pleural cavity.

Rapid inspiration of a drop of novocain placed in the shank of the needle or the production of a cough reflex on injecting the solution indicates that the needle tip has penetrated through the pleura. Aspiration should always be attempted before injection. If the needle lies within a blood vessel or the subarachnoid space aspiration of blood or spinal fluid makes these complications obvious. None of these possibilities is dangerous provided the condition is looked for and recognized and the position of the needle changed.

As soon as the needles are inserted in the correct position 2 cc of two per cent novocain-adrenaline solution should be injected into each. Following this and depending on the segments infiltrated, the characteristic signs of intercostal and sympathetic nerve paralysis should appear within a period of 15 minutes. In case the upper four thoracic nerves are blocked anesthesia should appear in the axilla a short distance down the inner arm and over the third and fourth ribs. No skin anesthesia develops over the first and second ribs as this region is also innervated by descending branches of the third and fourth cervical nerves. No anesthesia should develop in the hand but the entire arm side of the neck and head should become dry and distinctly hot. In addition to this an accurate injection of the first thoracic ganglion should produce a well defined Horner's sign. After injections in the lower dorsal region loss of sweating and intercostal nerve anesthesia coincide with the segments infiltrated.

In case these signs fail to develop the needles should be readjusted and an additional cubic centimeter of novocain solution injected into each but a total of 3 cc should never be exceeded. The reason for this is unimportant. Greater amounts of novocain spread so far in the tissues that they may produce characteristic signs of sympathetic paralysis whereas 5 cc of alcohol subsequently injected will fail to destroy the desired rami. When 3 cc of novocain fail to produce rapid and clear-cut paralysis it is better to withdraw the needles and try again on another day.

When satisfied that the needles are correctly placed it is best to inject 2 to 3 cc more novocain into each (one per cent novocain rather than two per cent). This supplementary infiltration is to ensure a wide spread anesthesia so that the final injection of alcohol will be painless. Some writers have advised the injection of alcohol under a general

anesthetic, claiming that this avoids pain on injection and prevents dilution of the alcohol. This technic loses the localizing advantages of the primary injection of small amounts of novocain. When additional novocain is injected secondarily up to a total of 5 cc. for each needle, a slow, careful injection of the alcohol is rarely painful. The argument that dilution of the alcohol prevents effective destruction of the nerves does not seem reasonable since 50 per cent alcohol is supposed to penetrate tissues better than 95 per cent.

The final injection of 95 per cent alcohol is carried out by instilling 5 cc. very slowly through each needle. It is well to test out each needle again by aspiration to make sure its tip cannot have moved and penetrated a blood vessel or a prolongation of the subarachnoid space. If the patient complains of any burning pain along the course of an intercostal nerve, the injection must be stopped for a few minutes until the discomfort subsides. By taking sufficient time it is usually possible to carry out these injections with little discomfort to the patient. In order to mark the position of the alcohol $\frac{1}{4}$ cc. of lipiodol may be injected through the highest and lowest needles. This minor addition to the procedure gives a very exact idea of the position of the alcohol at a subsequent x-ray examination. The needles are then withdrawn.

In order to minimize diffusion of the alcohol it is best to keep the patient as quiet as possible for an hour following the injection. He may then be permitted to shift over on his back and have the bed rest elevated to any angle that he desires. Most patients can be up in a chair on the following day and leave the hospital within 72 hours.

RESULTS AND SEQUELAE

Our records contain 37 cases in which cervicothoracic paravertebral block have been performed. Among these are but seven instances in which the procedure was carried through for relief of anginal pain. Four of these were completely relieved for 4, 5, 9, and 11 months. Three of these cases succumbed to their cardiac lesions without recurrence of pain. One patient cannot be traced. A fifth case was possibly 50 per cent improved for the two months he lived. In the other two cases, in which the procedure was used to stop anginal pain, the ganglia could not be successfully injected. Among these 37 cases a Horner's syndrome and increase in temperature in the corresponding hand lasting more than six months

was produced in 21. In seven evidence of sympathetic block was present for ten days to two weeks and then disappeared. In one case in which the injection was performed to relieve causalgia in the hand and arm a fatality occurred. Three needles had been introduced to block the first, second and third thoracic sympathetic ganglia. Aspiration of the needles showed that they were neither in the pleura, the subarachnoid space or a vein. Two cubic centimeters of two per cent novocain had been injected into the needle opposite the seventh cervical vertebral spine. As a Horner's syndrome appeared the patient complained of respiratory difficulty. In less than a minute his respirations ceased and could not be restored. Immediate autopsy showed that he had marked emphysema with upward distention of the dome of the pleura. The needle had crossed the pleural cavity in reaching the sympathetic chain. Death was ascribed to a pleuro-pulmonary reflex. My own opinion is that the needle tip might have slipped deeper as the novocain was injected and entered the subarachnoid space. In this way the novocain reached the medulla and caused a respiratory collapse. I have had referred to me two patients in whom alcohol had inadvertently been injected into the subarachnoid space during this procedure. In one instance a complete transverse lesion of the cord resulted, in the other marked weakness of the leg and mild sphincter disturbance.

Another unfortunate sequella of this procedure is a persistent neuritic pain due to irritation of the first or second thoracic nerves by the alcohol. Five of our 37 cases complained of this distress although fortunately it disappeared in four to six months. In six instances a mild pneumothorax in two combined with a slight friction rub and a slight amount of pleural pain was recorded.

I have had occasion to remove the cervicothoracic chain in two cases who had been injected four and seven months previously with apparent success. I could not see that the injection had produced adhesions which made subsequent ganglionectomy more difficult.

If successful alcohol block of the three or four upper thoracic sympathetic ganglia will relieve anginal pain. In experienced careful hands the procedure is safe. About 50 per cent of these patients can be completely relieved of their pain, another 30 per cent benefited. In these cases major surgery may impose too great a strain upon an already crippled myocardium. Paravertebral sympathetic block with alcohol

should be given primary consideration as a method for the relief of anginal pain

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CHAPTER XXXIX

USE OF QUINIDINE IN CARDIAC IRREGULARITIES

By WILLIAM J. KERR, M.D.

Introduction Further experience in the use of quinidine has shown it to be one of the most valuable drugs. The first wave of popularity was short lived due to the unwise selection of cases and to faulty methods of administration. The drug was tried in a variety of cardiac conditions and because of untoward results in a few cases its use was largely abandoned or greatly restricted in many clinics. The general practitioner has been reluctant to accept the drug and to acquire the knowledge which will assure him of the best results when properly chosen for treatment largely because of unwarranted fears which have been aroused concerning its dangers.

During the past ten years several authors have reported their end results after some years of experience. There is general agreement on the value of the drug in selected cases. Methods of administration have varied slightly. The dangers of toxicity have been reduced by a better understanding of their cause. Fewer accidents have resulted when certain contraindications are observed. Some authors have limited the use of the drug to cases of auricular fibrillation either of paroxysmal type or of recent onset. Digitalis has been given with quinidine or as a preliminary treatment before quinidine is begun.

I ACTION OF THE DRUG

The experimental studies on the action of quinidine and quinine compounds were summarized by Boyer¹ in 1908 and by many others in the past ten years. When acting directly on the heart the frequency of beats is diminished without producing irregularities. The excitability of the muscle is reduced by elongation of the refractory period and diminishing the number of contractions of the auricles and ventricles. The action upon contractility is the same for all muscular tissue bringing

about a decrease in contraction. Conduction is prolonged through an action on the cardiac muscle and conducting mechanism. The action on the extrinsic nerves of the heart is to reduce the excitability of the vagus and to paralyze the intracardiac endings. Other actions on the heart and extrinsic mechanism are suggested, but experimental evidence is conflicting on this point. The vascular actions are also somewhat uncertain. There may be some stimulation of the vasoconstrictors in small doses, but larger doses may show the opposite effect. Quinidine and quinine differ only quantitatively, the former being more active in the proportion of about two to one. Auricular fibrillation is brought to a termination because the refractory period is increased at a greater rate than conduction time is increased in the muscle—a view which has been held by Lewis and others. Haskell¹⁷ found experimentally that quinidine restored the normal cardiac rhythm after it had been disturbed by digitalis and attributed this to the action of the drug on the vagal endings and, to a less extent, to a direct influence on the myocardium. Gruber and Robinson¹⁸ found that hearts made to fibrillate by the action of papaverine or morphine were restored by injections of quinidine. It has been suggested that quinidine acts in an opposite manner to digitalis. Levine²⁴ showed experimentally in the normal cat that quinidine raised the threshold for the faradic current necessary to produce ventricular fibrillation.

II. INDICATIONS

The chief indications for the use of quinidine are now well known. The commoner irregularities of rhythm respond favorably. Such arrhythmias as *auricular fibrillation* and *auricular flutter* which are usually found in association with serious myocardial and valvular disease, offer the largest field for its use. Bouts of *paroxysmal auricular tachycardia* may be quickly terminated and further attacks prevented by its continued administration. *Extrasystoles*, and more particularly those arising in the auricles, are in many cases prevented. *Paroxysmal ventricular tachycardia* may be controlled, but its use in such cases has not been general. In more persistent ventricular tachycardia associated with coronary thrombosis where circulatory collapse is evident, quinidine has been given by the intravenous route with encouraging results in some cases. Its use in *coronary thrombosis* to prevent ventricular tachycardia and ventricular fibrillation has been recommended, but in the presence

of defects in the conduction system it is possible that such disturbance in mechanism would be produced by setting up a circus movement in the ventricles. In heart block quinidine is of doubtful value and in many cases would seem to be contraindicated through its action on the conduction mechanism.

III. CONTRAINDICATIONS

In general it may be said that *extensive myocardial disease* as shown by congestive failure and hypertrophy and dilatation of long standing is a contraindication for quinidine. If in any given case the underlying condition is such that the patient would not likely be any better off with a normal rhythm with the sinus rate more rapid than the ventricular rate under control by digitalis then such a drug should be withheld. In arrhythmias coming at the end stages of valvular disease of the mitral or tricuspid valves especially quinidine should not replace digitalis. If there is a history of *embolism* recent or remote quinidine should not be used although the dangers in such cases have been exaggerated. Some of the earlier writers failed to take into account the natural history of the disease and the great frequency of embolism in cases with hypertrophy and dilatation of the chambers of the heart from any cause in cases of coronary occlusion with mural thrombi and in cases of acute or subacute bacterial endocarditis. Inquiry should always be made of the patient concerning a possible *idiosyncrasy* to quinine when used in the treatment of other diseases. When susceptibility is demonstrated great caution should be used or the drug abandoned entirely. If symptoms of toxicity arise when the test dose is given the drug should be stopped. Such cases have not been observed in the writer's experience but are described. In partial or complete *heart block* in bundle branch block and in aortic oration block the drug should probably not be used or the patient should be watched closely and the quinidine stopped at the first sign of toxic symptoms. *Absence of fibrillation waves in the electrocardiogram* predicate unfavorable results wherever in those cases where coarse auricular waves are seen the results are best. In patients of *advanced years* there is less likelihood of success and greater danger of accidents.

There are exceptions to this rule as illustrated by the following case. An elderly patient of 78 years was one of a number of advanced years who had been under observation in a home for the aged and infirm. They had been known to have had auricular fibrillation of many years standing.

and had no marked symptoms due to the arrhythmia an observation frequently made in patients whose ventricular rate is not increased greatly by the disordered action of the auricles. Several of the group responded to relatively small doses of quinidine and in one a normal sinus rhythm was restored after a single dose of 0.2 Gm (3 grains) although the auricular fibrillation had probably existed continuously for 20 years.

IV TYPES OF ARRHYTHMIAS

Those arrhythmias in which quinidine is of value will be reviewed. In properly selected cases of *auricular fibrillation* the normal rhythm may be restored and the patient returned to a more useful life without great risk. When quinidine was first used it was thought that better results could be obtained if the arrhythmia was of short duration but longer experience has shown that while this is generally true, there are some cases where excellent results may be achieved after the condition has existed for many years. After a period of a month the duration is of little consequence. Paroxysmal auricular fibrillation may respond readily to small doses of the drug although there may be some uncertainty whether the attack would have continued without its use. In mitral valvular disease which is progressive it is not uncommon to see paroxysmal attacks of auricular fibrillation months or years before the arrhythmia becomes of the persistent type. In this early period attacks will often be prevented by constant use of quinidine. Paroxysmal auricular fibrillation is also common in degenerative cardiovascular disease and will respond to treatment. Since this disease is progressive auricular fibrillation tends to become persistent and later will fail to respond after several successful trials.

The experience reported in the following summary of a case history is not unusual. Mrs S B 45 years of age had had an attack of rheumatic fever 20 years previously. For a year she had experienced bouts of palpitation of great severity lasting for periods of a few minutes to about an hour with sudden onset and offset. Examination between attacks showed enlargement of the type usually seen in mitral valvular disease. There were signs of marked mitral stenosis and insufficiency. When seen during an attack the rhythm was irregularly irregular with a ventricular rate varying from 120 to 150 per minute. An electrocardiogram showed auricular fibrillation with coarse auricular complexes at the rate of 150 to 600 per minute. Quinidine sulfate was prescribed in doses of 0.2 Gm (3 grains) to be taken upon awakening in the morning and at bedtime. Two additional doses were advised to be taken at noon and at about

G P M For a period of four years the attacks could be prevented if she adhered strictly to this regime but if she missed a single dose of the drug an attack would supervene. At the end of this four year period attacks could not be prevented by much larger doses. Digitalis was then employed with satisfactory control for three years when death resulted from cerebral embolism at the age of 52 years.

In toxic thyroid disease auricular fibrillation appears in paroxysmal form in over a third of the cases and tends to be more persistent in a considerable number of them. The results are uncertain before treatment of the underlying condition but when the goiter is removed or other successful measures are instituted to reduce the toxicity the greatest hope can be offered for success. It is apparent that paroxysmal auricular fibrillation is less commonly seen now in patients with toxic goiter than a decade ago. This is probably due to the widespread use of iodine in the treatment of such patients.

Cases should be chosen for treatment where there is little or no congestive heart failure and if such failure be present suitable measures should first be taken to restore the circulation before quinidine is begun. In cases where there is no evidence of valvular or myocardial disease the results will be most gratifying. Auricular fibrillation arising in the course of acute infections or following operations responds favorably although here again the likelihood of spontaneous termination of the attack may lead to a false conclusion concerning the value of the drug. In many clinics the practice among surgeons of giving large amounts of fluids parenterally after operations to elderly persons frequently causes circulatory embarrassment. In such cases auricular fibrillation frequently arises. As a rule a single dose of quinidine will restore the normal rhythm but the fluids should also be restricted as much as is consistent with good postoperative management. If patients are greatly disturbed by the auricular fibrillation or are of nervous temperament a short course of bromides or other sedatives may be helpful before quinidine is begun.

In *auricular flutter* the normal rhythm may be restored in about 75 per cent of the cases. It is supposed that most cases of auricular fibrillation pass through a period of coarse fibrillation to a stage of auricular flutter before the normal rhythm is reestablished but this period is so short that it is seldom recorded. Better results may be expected if the arrhythmia appears in paroxysmal attacks when they may be abruptly terminated or subsequent attacks prevented. Auricular flutter arising in

the younger age groups with underlying valvular disease will respond better than in those past middle age with degenerative vascular disease. In view of the low percentage of successful results it has been the writer's custom to treat the patient with digitalis first to increase the auriculo-ventricular block and to bring about auricular fibrillation. Then when digitalis is withdrawn the normal rhythm is usually promptly resumed. If the normal rhythm is not reestablished quinidine can be expected to give excellent results in most cases. In patients with toxic thyroid disease in the course of acute infections or after operations the same favorable results may be expected as in auricular fibrillation.

In so-called *flutter fibrillation* good results may be expected. Personal experience has shown that patients with low auricular rates and prominent fibrillary or flutterlike waves as demonstrated by the electrocardiographic record respond most favorably to treatment whereas those in whom the evidence of auricular electrical activity is slight will be less likely to benefit by treatment.

Paroxysmal auricular tachycardia is usually unassociated with valvular or myocardial disease and in these cases good results may be expected either in stopping attacks or in preventing their recurrence. However unless the attacks are as frequent as once a week or tend to be of long duration or are very distressing to the patient the continuous use of quinidine is not necessary or desirable. There appears to be some tendency to an acquired tolerance to the drug with continued use in a few patients and it may then be ineffective when it is needed in more serious attacks. Likewise if larger and larger doses are required symptoms of toxicity may arise which would cause the drug to be abandoned. Similar experiences have personally been met with in paroxysmal auricular flutter and fibrillation and it is possible that the clinical reputation for an increased tolerance may be in part due to the progressive nature of the underlying disease which tends to produce more persistent arrhythmias.

Auricular and ventricular extrasystoles are in many cases eradicated by quinidine but it should be kept in mind that the treatment here is purely symptomatic. In those cases where there is discomfort because of the arrhythmia it may be useful. Where possible the factors responsible for the extrasystoles should be removed. In young persons without evidence of valvular myocardial or pericardial disease the continued use of quinidine should not be resorted to. In many cases of valvular

and myocardial disease, extrasystoles may appear months or years before the more serious arrhythmias, and in such cases the use of daily rations of the drug may be of value. Personal experience has shown that auricular extrasystoles are more amenable to treatment than are the ventricular types, although others have found little difference in the percentage of successful results. Sometimes quinidine may be combined with digitalis and other drugs with better results. Quinidine may be of value in suppressing ventricular extrasystoles arising in patients who are taking maximal doses of digitalis.

Extrasystoles arising in the auriculoventricular node and in the ventricular conduction apparatus may respond favorably to treatment but in the writer's clinic the results have not been good in a limited number of cases.

Nodal rhythm arising in the auriculoventricular node or junctional tissues is not likely to respond favorably to treatment with quinidine according to personal experience.

Ventricular tachycardia is usually associated with grave myocardial disease. The attacks are usually brief and paroxysmal in nature, but may continue until death, causing great distress. Quinidine has been used successfully in a number of such cases and its use here is justified for symptomatic relief and may be lifesaving. A high mortality may be expected in those cases associated with coronary occlusion, but if the conducting mechanism is damaged, it is possible that quinidine may further depress its activity and the condition may pass from one of ventricular tachycardia to ventricular fibrillation which, if continued for more than a brief period results in death. Some of the fatal results in the use of quinidine may be attributed to this action. Other drugs such as potassium salts, may be more useful in such cases.

In a *combination of arrhythmias* where there is widespread myocardial disease, the use of quinidine is seldom justified. It should not be used in complete heart block or bundle branch block associated with auricular flutter or fibrillation. In such cases an independent circus movement may be instituted in the ventricles, resulting in ventricular tachycardia and ventricular fibrillation.

V. METHODS OF ADMINISTRATION

The *oral method* has been found most suitable for administration. Quinidine sulfate is usually given in tablets, cachets or capsules. The

gelatin capsules are convenient to use and those containing 0.2 Gm (3 grains) of the drug are small and most suitable for ordinary cases. When the intravenous method is used, the sulfate of quinidine may be given in a five per cent solution in distilled water or other suitable solvent. The dosage by this method may vary, but amounts from 0.5 Gm ($7\frac{1}{2}$ grains) to 1.2 Gm (18 grains) have been employed, given slowly, and with due precautions, to be sure that the needle is in the vein and to stop when the arrhythmia is abolished or untoward symptoms appear. Hepburn and Rykert¹⁸ recommend up to 4.0 Gm (60 grains) in 500 cc (one pint) normal saline or five per cent glucose solution given at the rate of 100 to 120 cc ($3\frac{1}{2}$ to 4 ounces) per hour for persistent attacks of ventricular tachycardia where the drug cannot be given by mouth. Their results in controlling the attacks, relieving symptoms of shock and in promoting recovery of patients with coronary occlusion accompanied by ventricular tachycardia are very promising. Quinine dihydrochloride has been used intravenously in the writer's clinic for many years in doses of from 0.5 Gm ($7\frac{1}{2}$ grains) to 1 Gm (15 grains) in *paroxysmal auricular tachycardia* and in *auricular fibrillation* with good results. Padilla and Cossio³¹ and Hepburn and Rykert¹⁸ have given the larger doses of quinidine sulfate intravenously in *paroxysmal auricular flutter* and *auricular tachycardia* with good results but the writer has not been satisfied with the intravenous use of quinine dihydrochloride in *auricular flutter* perhaps because the drug has not been given in sufficient dosage. The incidence of severe toxic manifestations was rather high. In view of the excellent results with the oral administration of quinidine in the *paroxysmal auricular arrhythmias* and the more pronounced and sometimes unfavorable action of the quinidine compounds on the functions of the heart muscle, its intravenous use in such doses is not recommended except in obstinate cases. There is also an added danger of thrombosis in the veins of the arm with this method.

When given by mouth in cases where there is an absence of hydrochloric acid in the stomach quinidine may be better absorbed if hydrochloric acid is used. However no striking difference in results has personally been observed in such cases.

Quinidine is rapidly excreted from the body through the kidneys as was shown by Lewis and others. Wedd and Hubbard³² found that traces of quinidine could be demonstrated in the urine as long as 12

hours after the dose had been given but that traces of the alkaloid in the urine did not insure a therapeutic effect. The concentration of the alkaloid in the blood stream probably is an important factor in controlling the heart. On the basis of rapid absorption and excretion it has been the writer's practice to repeat the dose usually 0.2 to 0.4 Gm (3 to 6 grains) at frequent intervals when trying to terminate attacks of auricular fibrillation or flutter and to give it every three or four hours throughout the *day and night*. By this method results are achieved with a smaller total dose than by the method of gradually increasing dosage given only two or three times during the daytime or by a regular ration of 0.4 Gm (6 grains) three times a day. If results are not obtained the size of the dose may be increased but a rule should be made under such circumstances to see the patient personally before each succeeding dose is given. A failure on the first attempt does not contraindicate a further trial and sometimes successful results will be obtained after several failures.

The following notes from the case record of Mrs. E. J. aged 30 years will illustrate the author's preferred method for use of quinidine in the restoration of normal sinus rhythm in chronic auricular fibrillation. Upon entry to the hospital the patient exhibited the usual features of congestive heart failure with orthopnea, right hydrothorax, enlarged tender liver and edema of dependent parts. The heart was greatly enlarged and displaced to the left. There were signs of mitral valvular disease, probably rheumatic in origin. Auricular fibrillation was present and apparently had existed for six weeks. The fibrillation waves in the electrocardiogram were rapid and prominent. The ventricular rate was about 130 per minute. There were no signs of enlargement of the thyroid gland and no evidence of thyrotoxicosis. After a preliminary course of treatment with digitalis and other measures designed to restore circulatory efficiency had been unsuccessful the digitalis was discontinued. The ventricular rate was then 84 per minute. After a test dose of quinidine sulfate of 0.2 Gm (3 grains) which provoked no tinnitus, gastrointestinal symptoms or eruption the drug was given in doses of 0.4 Gm (6 grains) every six hours day and night. When 1.8 Gm (27 grains) had been given (the average dose required to restore normal sinus rhythm in well selected cases) the rhythm became regular and the electrocardiogram showed that the impulses were arising at the sinoauricular node. The P waves were somewhat distorted and diphasic in Leads II and III and the AV conduction time was at the upper limit of normal. The dosage of quinidine was reduced to 0.2 Gm (3 grains) every six hours and continued for a

week. Thereafter for three months four doses of only 0.2 Gm. (3 grains) were given each 24 hours. The first dose was given before arising and the last at bedtime. The other two doses were given at intermediate times but not more than six or seven hours apart. At the end of this three month period when there was no return of congestive failure or arrhythmia the drug was discontinued. During the subsequent two years there was no return of symptoms. However the physical activity had been reduced by change of occupation and avoidance of unusual physical and emotional strain. If there had been a return of the arrhythmia during this period the same procedure could have been repeated after which experience the drug would have been given continually at six hour intervals until persistent auricular fibrillation would arise because of advancing myocardial insufficiency at which time digitalis would be substituted.

When giving quinidine as a prophylactic treatment for extrasystoles or paroxysmal auricular arrhythmias the patients may be ambulatory but in the more persistent and serious arrhythmias the patient should be under careful control in bed and if possible the course of treatment should be followed closely with frequent electrocardiograms. Evidence of progressive conduction defects or new and abnormal rhythms arising in the junctional tissues or ventricles should contraindicate further use of the drug.

Digitalis has frequently been employed as a preliminary treatment and is now used to some extent in conjunction with quinidine. As previously stated if there is congestive failure of moderate or marked degree it is probably unwise to attempt restoration of sinus rhythm until after this condition is relieved. In the early days of quinidine therapy it was used in some such cases with success which however was often very temporary. Digitalis or similar compounds should be given by the usual methods and other measures should be taken to restore the circulatory efficiency. The digitalis should then be stopped for two or three days and quinidine begun. If unsuccessful after a period of a few days another course of digitalis may be given and the attempt repeated as before as suggested by Linn and his co-workers.²⁷ If then unsuccessful digitalis may be given in combination with quinidine. In cases with prolonged auriculoventricular conduction time it would seem unwise to give digitalis which would tend further to increase the block in which instance quinidine may still further depress the conducting apparatus with unfavorable results. It is doubtful if quinidine should be used at all in

such cases Quinidine may be useful in controlling ventricular extrasystoles and coupled rhythm resulting from digitalis. Digitalis is sometimes of value in preventing extrasystoles associated with myocardial disease before a course of quinidine is instituted for the relief of other arrhythmias.

After the normal sinus rhythm has been restored the drug may be discontinued at once or the patient may be put on small daily rations. Some of the early failures to maintain a regular rhythm were due to a withdrawal of the drug as soon as the arrhythmia ceased. Further experience has shown that better results can be had by giving small doses daily or preferably several times a day over a period of time. It will usually be found that three to four doses each of 0.2 to 0.4 Gm. (3 to 6 grains) a day are most effective. In some cases two doses, one in the morning and one at night, will suffice. In a few cases, however, better results will be attained if a double dose is given at bedtime or if the patient is awakened at night for an additional dose. Many patients are able to take small doses over a long period of time without harmful effects. In others toxic symptoms may arise such as tinnitus or gastrointestinal symptoms with troublesome diarrhea which prevent further medication. In rare instances the writer continued the drug in the face of a tinnitus and he has been pleased to have this symptom entirely disappear. If the object is to prevent the recurrence of frequent and paroxysmal attacks of arrhythmias the treatment must be given as described above. If attacks are infrequent an individual plan of administration of the drug is desirable. Usually a moderate dose will then terminate the attack. Each patient after a little experience will learn when and how to get the best results. Some patients find the need for the drug greatest when they are about to undergo an unusual physical or mental strain and ration themselves accordingly.

It should constantly be kept in mind that the serious irregularities are usually associated with progressive cardiac disease and that at best it cannot be hoped to prolong the normal cardiac beat indefinitely. In such cases it is more profitable to use digitalis or other drugs. Where the arrhythmia is transient and arises in the course of toxic thyroid disease or with infections or after operations there is usually no further need of the drug when the general condition of the patient is improved. In toxic goiter there may be a return of the arrhythmia with recrudescences.

cences of the disease which will in turn respond after treatment of the gouter

VI TEMPORARY AND ENDURING RESULTS

1 AURICULAR FIBRILLATION

In 1928 there appeared several important papers dealing with the results in the treatment of *auricular fibrillation* with particular reference to enduring results. It is difficult to compare these statistics because of the variability in the selection of cases in the methods of administration and in the after treatment when normal rhythm had been reestablished. Maynard²⁸ in a series of 53 cases had success in 71.7 per cent. Of 35 cases followed five years or more 25 had reverted to permanent arrhythmia which could not be controlled by quinidine and in only six cases was the normal rhythm continued in four other cases the normal rhythm persisted until death. This author obtained the best results when the drug was given in moderate doses every four hours day and night. *An advancing morbid process was largely responsible for failure to maintain a normal rhythm.* A total of 47 Gm (1½ ounces) was required in one case although in most cases normal rhythm was restored before 10 Gm (2¼ drams) had been given. In two cases 0.4 Gm (6 grains) sufficed. Spiro and Newman²⁹ reported 80 per cent of successful results in a series of 41 selected cases. A good ventricular contraction under fluoroscopic examination was considered a favorable sign before beginning treatment. Quinidine was given in increasing doses up to approximately 5 Gm (75 grains) during the 24 hour period (day and night). If unsuccessful the quinidine was stopped and after a brief course of digitalis (one to three days) was repeated. If again unsuccessful another trial was made after an interval of one or two months. When normal rhythm was reestablished a dosage of 0.6 Gm (4 grains) was continued three times a day.

In 1930 Newman and Spiro³⁰ gave a detailed report on the use of quinidine sulfate for persistent *auricular fibrillation* after an experience over a period of six years and added 25 cases to their former series. Among 40 patients whose subsequent history was known 12 reverted to *auricular fibrillation* before the end of one year 28 maintained normal sinus rhythm for one year or more 23 for two years or more 11 for three years or more eight for four years or more three for five years or more and two for over six years. Among 66 patients treated three died within

a few hours following restoration of the normal sinus mechanism presumably from embolism three more were alarmingly toxic probably with ventricular tachycardia or fibrillation and six others were moderately toxic. They advised against the use of quinidine in elderly persons with weakly contracting hearts or in those with mitral lesions and very large left auricles. The method of selection of patients for treatment was not stated. These writers reported 82 per cent of restorations of sinus rhythm among 66 patients treated.

Braniwell and Ellis²⁷ at the Manchester Royal Infirmary properly stressed the requirements of the drug as to be of value. Its usefulness is to be tested by the duration of the reestablished normal rhythm, the benefits to be derived and the dangers incidental to its use and not by its action in restoring the normal rhythm. In a group of 27 unselected cases except for the exclusion of the toxic thyroid cases treated during the six years previous to 1906 and under observation for a period up to five years there was definite and lasting benefit in nine cases or 31 per cent. In an additional ten cases there was only transitory benefit. In eight cases or 29 per cent quinidine failed to restore the normal rhythm. In 22 of the cases there was probably a rheumatic background and in the remaining five cases there was chronic myocardial disease. Many cases were included early in the study which would now be treated with digitalis. Quinidine was administered in doses of 0.4 Gm. (6 grains) every two hours for five doses and generally the normal sinus rhythm was restored on the first day. If necessary the dosage was continued for two more days. After normal rhythm was restored no further quinidine was recommended unless a relapse occurred when the drug was to be continued in reducing doses for several weeks after a second response. If further relapses occurred the drug was to be continued indefinitely.

Iron, Blondel and Viau²⁸ treated successfully 39 of 81 cases (48 per cent) of auricular fibrillation. In 30 of these 39 cases the normal rhythm continued except in five cases. In two of these there were brief periods of tachycardia responding easily to quinidine and in three others auricular fibrillation reappeared and was permanent after four years, two years and seven months respectively. In the 25 remaining cases the arrhythmia had not reappeared after a long time. In nine additional cases normal rhythm was maintained for periods from five days to about three months and were not included in the series but if included would bring successful ter

mination of the attack to about 60 per cent. During treatment the drug was given in doses of 0.2 Gm. (3 grains) in increasing number during the day until about 1.2 Gm. (18 grains) was given daily. If unsuccessful after about ten days, the drug was omitted and after a period of four to six weeks digitalis was given for one or two weeks and quinidine was resumed, increasing the dose faster and giving up to 1.6 Gm. (24 grains) a day. If again unsuccessful, another period of rest was allowed and the quinidine repeated without a preliminary course of digitalis, and doses of quinidine increased to a maximum of 2.0 Gm. (30 grains) a day. After attacks were terminated, the dosage was gradually reduced but divided into four or five doses a day. Digitalis was recommended from time to time for periods of a few days. Blood pressure readings were taken during treatment. Electrocardiographic control was advised. Atropine was suggested for troublesome bradycardia at the end of the treatment.

Parkinson and Campbell³³ reported the results in 20 cases of paroxysmal auricular fibrillation and in 44 cases of established auricular fibrillation. Among 19 of those with paroxysmal attacks, nine patients were much improved and the attacks were abolished or greatly reduced. In five cases there was only temporary benefit and in the remaining five cases there was no improvement. In 44 cases of established auricular fibrillation the normal rhythm was restored in 30 or 68 per cent. In 23 of these cases the rhythm was maintained for an average of two years and in one case after five years. Four patients had temporary relapses, again responding to treatment. In the seven remaining cases, the normal rhythm was maintained for an average of 18 months. Relapses were more frequent on reducing the quinidine rations. Results were better where there was no progressive valvular disease or in the absence of toxic goiter. In about one-half of the reported cases there was a rheumatic background. With two exceptions, the patients were benefited by the restoration of normal rhythm. The dosage in paroxysmal cases was 0.3 Gm. ($4\frac{1}{2}$ grains) twice daily, and in the established cases an initial dose of 0.3 Gm. ($4\frac{1}{2}$ grains), followed by daily increase in dosage of 0.3 Gm. ($4\frac{1}{2}$ grains) until 2.0 Gm. (30 grains) were taken daily. *Congestive heart failure* was treated with digitalis before administration of quinidine; but digitalis and quinidine were not given at the same time.

Wolff and White⁴² reported the results of seven years' experience with quinidine sulfate from 1921 to 1928. In 62 cases of persistent auricular

fibrillation and eight cases of auricular flutter, the normal rhythm was restored in 65.7 per cent. The results were best (100 per cent) in those patients with apparently normal hearts, irrespective of age or duration. The next most satisfactory results were obtained in patients under 41 years of age with *rheumatic heart disease*. In *toxic goiter* the results were better than in the hypertensive and arteriosclerotic groups. If the arrhythmia had persisted for more than a month, the duration had little influence on the outcome. Failures were found to be due to insufficient dosage, infections, and possibly alcoholism. Digitalis in full doses was suggested as a preliminary measure. The most frequent change in mechanism was to auricular flutter, but in no case was this mechanism of the fixed type. In three cases there was probable auricular standstill and it was suggested that standstill of the entire heart may be a cause of some of the fatalities in treatment. The end results in a considerable number of cases indicated that health was promoted but that life was probably not prolonged by quinidine therapy. In treatment after preliminary digitalization, quinidine was recommended in doses of 0.38 Gm (6 grains) every two hours, five times a day until results were obtained or until toxic symptoms appeared. If unsuccessful after five to seven days, the drug was discontinued. If normal rhythm was restored, patients were given rations of from 0.19 to 0.58 Gm (3 to 9 grains) as long as they were in the hospital and after ward at home for a few weeks, when an attempt was made to get on without it. White has summarized his experience with this drug in his admirable text on heart disease.

Harris¹⁶ reported the end results in successful cases treated from 1921 to 1923 in the clinic of Sir Thomas Lewis. Cases with severe degrees of congestive heart failure were excluded. In 26 of 13 consecutive cases of chronic auricular fibrillation (60.5 per cent) normal rhythm was re-established. Of these 26 cases there was reversion to auricular fibrillation within a month in nine cases; at the end of six months in two more cases; at the end of one year in five more; and at the end of two years in an additional three cases, leaving only seven of 26 cases with normal rhythms at the end of two years. Of the seven remaining cases, auricular fibrillation reappeared in four more after 2, 3¼, 4½ and 7 years, respectively. One patient who was lost track of in 1926, had been regular for 1673 days; another remained normal to date (four years), and another one who was lost had been regular for 317 days. The low percentage of permanent

results in some clinics is probably due to a cessation of treatment when normal rhythm has been restored. On the other hand it is of interest that some authors have reported 25 per cent of patients with regular rhythm at the end of a year and 15 per cent at the end of two years. The selection of cases however varied greatly in different clinics so that results are not entirely comparable.

Chrilton⁸ advised a preliminary course of digitalis to slow the ventricular rate and to restore compensation. He advised a rational method of giving quinidine in moderate doses day and night. After restoration of normal rhythm small doses of quinidine two or three times a day were advised and to be supplemented by digitalis in small doses. It was pointed out that patients may be more uncomfortable with a normal rhythm than with the auricular fibrillation.

Hurxthal¹⁰ in 1930 had excellent results with quinidine in 59 cases of *goiter* with postoperative paroxysmal auricular fibrillation and in 55 cases of established auricular fibrillation all associated at one time or another with hyperthyroidism. In the paroxysmal type there were no failures. In the more persistent type the arrhythmia terminated spontaneously in seven cases. In eight cases quinidine was not used and in five cases its use was unsuccessful. In 34 cases the results were satisfactory. The drug was given in doses of 0.4 Gm (6 grains) every two hours until the pulse became regular or until toxic symptoms appeared or until a total of 2.5 Gm (39 grains) had been given. The use of 0.1 to 0.6 Gm (6 to 9 grains) after meals for several days was recommended for a second trial. When normal rhythm was restored a daily dose of 0.4 Gm (6 grains) was given for a month or so to insure permanency. Recurrences were attributed to a return of toxicity of the goiter or to coincident cardiovascular disease. *It is of interest that a series of patients with goiter with established fibrillation at the time of operation from two to seven years previously were recalled for examination and it was found that they had reverted to a normal rhythm. No quinidine had been given in these cases.*

Anderson¹ in 1937 recommended the use of quinidine on the third or fourth postoperative day in *thyrotoxicosis* if auricular fibrillation persisted. In a series of 23 cases the normal mechanism was restored by this method in 22 patients (96 per cent) in contrast to a lower percentage of favorable results in 16 patients treated later where the normal rhythm was restored in only ten patients (60 per cent). Quinidine was given as

follows. A test dose followed by 0.3 Gm (5 grains) each four hours day and night if the rhythm was not restored the dose was increased to 0.5 Gm (5 grains) each three hours and then if necessary, a dose was given each two hours.

Wedd³⁹ in 1929 summarized his results after several years of experience in England and in the United States. The oral method of administration was preferred. When given by mouth a reduction of the cardiac rate could be detected in about 15 minutes and a maximum effect was noted in two or three hours. On the basis of rapid absorption and excretion the suggested interval between doses was not more than six hours. The maximum single dose advised was 0.8 Gm (12 grains). For continuous administration doses of 0.2 to 0.4 Gm (3 to 6 grains) every three to six hours were given day and night. Quinidine and digitalis were given together to reduce the auricular rate and to keep the ventricular rate down during the period of treatment. This author held the opinion that the behavior of auricular fibrillation and flutter supports the circus movement theory of the mechanism involved in these arrhythmias. In hypertension cases with paroxysmal auricular fibrillation very poor results were obtained. Patients with toxic goiter responded better after operation. Attacks coming on after operations usually were controlled. In persistent auricular fibrillation best results were obtained in patients free from congestive heart failure and without evident valvular or myocardial disease; better results in the young than in the elderly (its use was not recommended in old persons with arteriosclerosis); better in those with small hearts and in those when the onset of the arrhythmia was recent. The expected duration of normal rhythm after restoration and the risks to be taken were important considerations before treatment was started.

Maynard²⁹ in 1931 in summarizing his own experience and that of others suggested that although from 50 to 70 per cent of patients with chronic auricular fibrillation may have the normal rhythm restored by quinidine the relief is only symptomatic. The patients selected should be those (1) to whom the arrhythmia is a symptomatic disturbance (2) with auricular fibrillation for one month or less by preference (3) in whom there is no congestive heart failure and (4) who do not have advanced mitral stenosis where recurrences are likely or where auricular thrombi are more likely to occur. In this author's experience patients with *rheumatic heart disease* responded better than those with arterio-

sclerosis, and patients with *thyrotoxicosis* showed excellent results. Quinidine was given in a dosage of 0.4 Gm. (6 grains) each four hours day and night and increased if necessary, followed by 0.2 Gm. (3 grains) three times daily for weeks or months after conversion.

Kohn and Levine,²³ in 1935, analyzed 45 cases of persistent auricular fibrillation from their own experience and reviewed the literature. The reversion to normal rhythm was held not to be the only criterion of success. They found patients with valvular heart disease (rheumatic) more resistant than patients without valvular disease. Patients with *thyrotoxicosis* after operation responded almost invariably to the drug. Older patients and those with long standing arrhythmia were more resistant and more liable to thrombosis and embolism. The indications suggested for the use of quinidine in chronic auricular fibrillation were: (1) The presence of the arrhythmia in an otherwise normal heart; (2) its persistence after operation in hyperthyroidism; (3) where the irregularity is the cause of intractable palpitation; and (4) in certain hopeless cases where other forms of therapy fail.

Hines and Maher,¹⁹ in 1933, gave a report on 28 ambulatory patients with auricular fibrillation. Quinidine and digitalis were given simultaneously in most cases. The drug was given in divided doses, and a total of not more than 0.8 Gm. (12 grains) was given daily. In 12 patients (41 per cent) the normal sinus rhythm was restored, and among those where failures occurred there were some who failed to cooperate.

Weisman,⁴⁰ in 1932, in a series of 28 ambulatory patients with auricular fibrillation treated with quinidine, reported 60 per cent of the results to be satisfactory. Digitalis was used in preparation, and as the dosage of this drug was diminished, the administration of quinidine was begun in very small doses and continued in small doses for a longer time than usual. In a later report,⁴¹ in 1936, of 17 successfully treated patients, five have remained regular for from four to five years.

Bulte and Reinwein,⁶ in 1930, using Bergmann's method of dosage, had normal rhythm reestablished in 67.3 per cent of 58 cases of all types treated. These authors summarized the immediate results in auricular fibrillation as reported by 30 authors. In a total of 1152 cases treated, the rhythm became regular in 618 cases or in 56 per cent. These figures include some of the figures from early reports, when cases were not so

carefully selected or when the drug was not continued after the reestablishment of the normal rhythm

2. AURICULAR FLUTTER

The immediate and enduring results in cases of *auricular flutter* have not been so brilliant as in *auricular fibrillation*. Previous to 1928 it was the general experience to have attacks terminated by quinidine in from 20 to 25 per cent of cases. In the past ten years there has been little indication that this percentage of good results has been materially increased, except by the use of excessive doses or by heroic and probably dangerous dosages by the intravenous route. In the past, most clinicians have been satisfied with the use of digitalis in converting an auricular flutter to auricular fibrillation when, if the digitalis is withdrawn, the heart will usually revert to the normal rhythm. If it does not, the patient is usually more comfortable and more easily controlled by continued use of digitalis. Since the advent of quinidine it has been the writer's experience that if the patient does not respond promptly to moderate doses of quinidine, it is safer and more satisfactory to proceed with digitalis, in the hope that auricular fibrillation will ensue, when the digitalis is omitted and quinidine is used after a period of two or three days. Uniform success was obtained in restoring the normal rhythm in this manner in obstinate cases if the flutter was successfully converted into fibrillation first by digitalis. A very few cases were observed where all attempts failed to abolish the original attack of flutter which had existed for two or more years in patients with fairly sound hearts. Lian and Viau²⁷ advised a similar plan of treatment. In paroxysmal auricular flutter better results can be expected by quinidine alone, unless there is congestive failure, in which case digitalis should be employed. Wolff and White⁴² found digitalis of more value than quinidine in auricular flutter. Bourne³ reported a single case of auricular flutter in a patient with mitral disease and tricuspid insufficiency, where enormous doses of quinidine were required to restore the normal rhythm. The attack had persisted for two years and after a preliminary course of treatment with digitalis for six weeks, quinidine was begun. Toxic symptoms appeared after a total of 33.3 Gm (500 grains) had been given. Quinidine was then combined with digitalis, but twice stopped after toxic symptoms developed. Then another course of quinidine alone, in moderate doses, was given and after three days normal rhythm was reestablished. A total of 50 Gm (750 grains)

was given during the course of treatment. On rations of 0.26 Gm. (4 grains) three times a day, the heart had remained regular for two months.

One would hesitate to continue the use of quinidine in such an obstinate case, and would perhaps try to convert the flutter to fibrillation if the patient was in great discomfort from the flutter rhythm. This author also advised this procedure in auricular flutter and recommended quinidine to restore the normal rhythm when auricular fibrillation appeared in such cases after the use of digitalis Wedd,³⁰ in 1929, reported four cases of auricular flutter treated with quinidine by mouth with nice successful result. In two other cases the attack stopped, but it was doubtful whether the quinidine played any rôle in the result. This author cited the nine cases of Singer and Winterberg with success in six after the intravenous use of quinidine Wedd expressed the opinion that auricular fibrillation should be avoided in the treatment of auricular flutter by digitalis as it may become permanent. As stated above, the writer does not consider this to be a serious matter, in view of the ease with which such cases revert to normal rhythm with quinidine.

Padilla and Cossio³¹ advised the use of intravenous quinidine in five per cent solution for various arrhythmias. The usual dosage was 0.5 Gm. (7.5 grains) for patients of 60 to 80 kg. (132 to 176 pounds). If unsuccessful, the treatment was repeated in 24 to 48 hours and the dose increased to 1.0 Gm. (15 grains). They gave as much as 0.15 Gm. (2¼ grains) per 10 kg. (22 pounds) without serious accidents. Patients were recumbent and quiet during administration of the drug. They have been successful in controlling attacks of auricular flutter. In these cases the ventricular rate was reduced. After normal rhythm was restored, quinidine was given by mouth to prevent a recurrence. Better results were obtained in the paroxysmal attacks. Later, these authors³² reported successful results from the intravenous use of quinidine sulfate in two patients with prolonged attacks of paroxysmal auricular tachycardia and two cases with auricular flutter. The general symptoms of toxicity were troublesome.

Tung Chen-Lang³ advised the use of digitalis and quinine simultaneously in the treatment of auricular flutter. The result was successful in a patient suffering from malaria.

Borg² suggested the use of quinidine sulfate in paroxysmal irregularities of the heart which cannot be diagnosed accurately because of their fleeting character and before persistent arrhythmias supervene.

Gold, Otto and Satchwell¹⁴ reported on the use of quinidine sulfate in a series of 21 patients with paroxysmal auricular fibrillation and flutter. They did not find that the ambulatory patients showed such satisfactory results as reported by other authors. It was their opinion that small maintenance doses of quinidine were of little value in preventing attacks and probably of little value in maintaining normal rhythm after it had been restored after prolonged attacks. They gave a detailed report of a patient with bundle branch block and attacks of auricular fibrillation and flutter. Continued use of the drug over long periods reduced the symptoms accompanying attacks probably because the auriculoventricular conduction system was influenced by the drug so that the ventricular rate was kept near the normal level. This patient later was able to tolerate 5 Gm. (60 grains) of quinidine sulfate daily for a year during which time there were no attacks.

Jourdonais and Mosenthal²² described the effects of quinidine in a 66 year old male who showed auricular flutter and complete auriculoventricular block. The auricular rate was 270 and the ventricular rate 36 per minute. While under daily treatment with quinidine and following 2.4 Gm. (36 grains) on a given day he developed nausea and gastric distress. It was found that the auricular rate had dropped to 130 per minute and the ventricular rate was increased. After further administration of the drug a temporary period of sinus rhythm was observed with a rate of 40 per minute with a P-R interval of 0.75 second. The present writer observed a similar example of profound influence of quinidine on the auricular rate in auricular flutter with the flutter waves falling from a rapid rate to 100 per minute. When the auricular rate falls to extremely low rates the functional auriculoventricular block tends to disappear.

3. PAROXYSMAL AURICULAR TACHYCARDIA

Here the results are very satisfactory in a limited number of cases. This arrhythmia is seldom associated with valvular or myocardial disease and only rarely is there a fatal outcome when the attacks persist for many days or weeks. If the patient has no discomfort during the attacks it is unnecessary to resort to treatment which may itself produce symptoms.

In those patients whose attacks are either frequent or of long duration (hours or days), or are accompanied by distressing symptoms and are not relieved by ordinary and well known measures, the use of cinchona compounds is justified. If the attacks threaten life because of their duration and associated congestive failure, the intravenous use of quinidine sulfate by the method of Padilla and Cossio may be tried, but personal experience has shown that this emergency seldom arises. Soluble quinine preparations are available and are generally effective.

Since January, 1923, quinine dihydrochloride has been used in the writer's clinic for the relief of obstinate attacks on the suggestion of Dr. E. L. Brick, of the staff, who studied under Winterberg, in Prof. Wenckebach's Clinic in Vienna, where this method had been employed for about two years. This drug is given intravenously in a ten per cent solution, slowly, watching for any untoward symptoms. The cardiac rate is usually promptly slowed when the injection is begun and in most cases the attack terminates before the full dose is given. The writer has not given more than 0.5 Gm. (7.5 grains) at a single dose. There may be a local burning sensation in the arm and a general feeling of warmth, but usually there are no other toxic symptoms. This method has rarely failed in a large series of cases. For prophylactic treatment quinidine sulfate by mouth is employed in doses of from 0.2 to 0.4 Gm. (3 to 6 grains) every six hours, giving at least three doses a day at first and gradually reducing the size of the dose if possible thereafter. If attacks are not prevented by moderate doses given in this manner, a double dose is given at bedtime or an extra dose given just before any unusual physical or mental strain is about to be undertaken. Bromides may also be given for their general quieting effect in this type of individual. Morphine, digitalis or potassium may be of value in these cases, but the use of opiates has been avoided because of the recurrent nature of the disorder. The value of quinidine in any given case can actually only be determined by several control periods when no drug is taken and by keeping a careful diary of the number and duration of attacks in the periods with and without treatment. In a few cases good results have not been obtained. In these cases it is usually a persistent diarrhea which appears, when moderate doses are given over a long period of time, to defeat the attempt at further medication.

Lian and Vian²⁷ reported a series of 27 cases of paroxysmal auricular tachycardia treated in the course of attacks or in the interval with good results in 22 cases. The drug was given by mouth in all but one case where the intravenous method was used. Wolff and White⁴² found quinidine of value in some cases of paroxysmal auricular tachycardia. Charlton⁸ had the same experience. Padilla and Cossio^{31, 32} advised the intravenous use of quinidine sulfate in doses of from 0.5 to 1.2 Gm ($7\frac{1}{2}$ to 18 grains) for attacks of this arrhythmia. It would appear that this dosage is too large and that if the drug is to be given intravenously the dose should be as small as possible, be given very slowly with electrocardiographic control and only after the usual simple methods of terminating attacks have been tried.

4 EXTRASYSTOLES

Ordinarily these do not require treatment with cinchona compounds. Measures should first be taken to exclude toxic causes such as digitalis, alcohol, tobacco, coffee and tea in excess, cerebral diseases, abdominal conditions associated with gaseous distention, local pulmonary or pericardial infections and lastly valvular or myocardial diseases where extrasystoles may be the earliest sign of impending arrhythmias of a more serious nature. In young persons under 30 years of age extrasystoles are so common as to excite no comment or ordinarily to require no special treatment. In older persons where extrasystoles arise from multiple foci in the heart or are increased in number on effort a more serious problem is at hand.

If extrasystoles persist after the usual causes have been removed and make the patient uncomfortable bromides or belladonna should first be tried for relief. Rest and digitalis in small doses may also be beneficial over a period of time. Prof. Wenckebach in 1924 suggested quinine sulfate and strychnin in capsule form two or three times a day and this combination has been found beneficial in some cases. Quinine or quinidine may also be given with digitalis in small doses. When giving quinidine alone for control of extrasystoles it is the writer's custom to give from 0.2 to 0.4 Gm (3 to 6 grains) three times a day giving one dose on awakening in the morning, one at bedtime and a third during the midafternoon. Sometimes a dose night and morning will suffice but occasionally it will be necessary to give the drug every four hours day and night for relief. When the extrasystoles are under control the

minimum effective dose should be determined and patients may be kept on the drug indefinitely. Only rarely will it be necessary to rely on this drug if the causes which tend to bring on the irregularities can be eradicated. Coupled rhythm or extrasystoles arising during the course of digitalis therapy may respond to quinidine.

Lian and Blondel²⁷ used small doses of quinidine to control extrasystoles and had the most favorable results in patients without myocardial insufficiency. If myocardial insufficiency was present digitalis was first given for a few days and stopped while the quinidine was being taken. In patients with bradycardia and extrasystoles quinidine was not advised. Their results on the whole were good. Wedd³⁹ found that extrasystoles usually disappeared after 0.6 to 0.8 Gm. (9 to 12 grains) given at a single dose and that daily rations of 0.4 to 0.6 Gm. (6 to 9 grains) may control the irregularity. The use of quinidine for treatment of these irregularities was not generally recommended in view of the beneficial results with bromides and belladonna. Wolff and White⁴² found quinidine of some value in the treatment of extrasystoles. Charlton⁸ had similar results and found that in some cases extrasystoles would not reappear after stopping the drug.

5 NODAL TACHYCARDIA

The results in the treatment of nodal tachycardia have not been gratifying. This arrhythmia originating in the auriculoventricular node or junctional tissues is usually associated with the more serious myocardial diseases the outcome of which is always uncertain. Digitalis would be preferred to quinidine in this instance in addition to the usual methods in caring for such a patient. Theobromine compounds may be a helpful adjunct.

6 VENTRICULAR TACHYCARDIA

This type may be successfully treated by quinidine although here as in the case of nodal tachycardia the underlying grave cardiac disease will frequently advance to close the issue even if the tachycardia is controlled. In the early days of quinidine therapy Kerr and Bender reported a case where auricular fibrillation and complete heart block existed together in an elderly man and in whom it was proposed to test the action of the drug on the isolated ventricle. On the first occasion the patient developed attacks of syncope resembling Adams Stokes syndrome but no records could be obtained to show what was taking place in the ventricles.

At a later date with more careful observation the test was repeated. There was a recurrence of the attacks and electrocardiograms and careful observations were made during the attacks which proved to be associated with brief runs of ventricular tachycardia and ventricular fibrillation. The writer was the first to suggest that circus movements similar to those in auricular fibrillation were probably set up in this case when the conducting mechanism was further depressed by the action of quinidine. Fortunately the patient survived these attacks which continued intermittently for several hours and lived for about seven years thereafter. The action of the drug in reducing the irritability of the heart muscle and in blocking the impulses in the conduction system would appear to preclude its use in patients with marked degrees of block in the conducting mechanism. Some of the sudden deaths described are probably on the basis of ventricular standstill or systole of the entire heart. Boyer⁴ suggested the possibility of ventricular standstill or ventricular fibrillation when the auricles became regular as the cause of sudden death. Levine and Stevens⁶ reported a case where ventricular tachycardia followed auricular fibrillation associated with coronary thrombosis. After quinidine in large doses of from 0.6 to 1.5 Gm (9 to 22½ grains) every several hours over a period of days the ventricular tachycardia was controlled. The maximum dose finally given was 1.5 Gm (22½ grains) five times in one day. These authors supported the view of Scott that quinidine increases the refractory period of the ventricular as well as the auricular muscle. There was apparently no evidence of intraventricular block in their case. Three other cases of coronary occlusion were mentioned where quinidine restored the rhythm to normal. Levine and Fulton⁵ reported ten cases of cardiac disease with ventricular tachycardia where quinidine was given by mouth or intravenously. In eight cases there was an associated coronary occlusion; in one there was a chronic mitral valvulitis but in the other case there was no evidence of organic cardiac disease. Quinidine was given in increasing doses up to a maximum of 1.5 Gm (22½ grains) five times a day in one case. The normal rhythm returned in eight of the ten cases. Afterwards quinidine was continued in small doses of from 0.3 Gm (3 grains) to 0.6 Gm (4½ grains) three times a day. In one case it was necessary to continue the drug to an amount of 1 Gm (36 grains) daily for months. Seven of the patients died and in most cases after an interval

of several days following the discontinuance of the quinidine. Of the seven fatal cases four showed coronary thrombosis, one ruptured heart, one cerebral embolus, and one lobar pneumonia.

Charlton⁸ reported a case of ventricular tachycardia responding to four doses of 0.4 Gm. (6 grains) of quinidine. Davis and Sprague¹⁰ reported a case where syncopal attacks and death occurred in the course of quinidine therapy. The patient was suffering from rheumatic heart disease and auricular fibrillation. A course of digitalis was followed by quinidine and a total of the latter drug of 8.2 Gm. (125 grains) was given over a period of four days when syncopal attacks associated with ventricular tachycardia appeared previous to death. It is likely that both digitalis and quinidine depressed the conducting mechanism in this case to bring about auricular standstill and complete block, and were responsible for the ventricular tachycardia. Spiro and Newman^{3c} advised against the further use of quinidine in patients where extrasystoles develop arising in the course of treatment as ventricular tachycardia may result and if the latter should be noted the drug is to be stopped at once.

In the past few years a number of reports have appeared on the action of quinidine in preventing or terminating attacks of ventricular tachycardia. Small doses of the drug have been recommended for patients early in attacks of coronary occlusion to prevent abnormal mechanisms in the ventricles. No adequate proof has been offered that the drug is effective for this purpose. Escamilla¹² studied a patient who had numerous attacks of ventricular fibrillation for over seven months and was unable to prevent attacks consistently by the use of quinidine. The present writer has had similar experience in a young man with paroxysmal ventricular tachycardia who was followed carefully for several years. Woodruff⁴⁴ however, after extensive experience with quinidine at the Cook County Hospital in Chicago, recommended the drug in small doses to prevent both ventricular tachycardia and fibrillation. The dosage advised for attacks was much larger than that given in other clinics and unusually large doses were given intravenously without any apparent ill effects. Hepburn and Rykert¹⁸ advised the use of quinidine sulfate in patients with *coronary thrombosis* who showed protracted attacks of ventricular tachycardia. The drug was used only after other measures failed. When gastric symptoms or shock prevented the use of quinidine by mouth the intravenous route was used. The average dose given intra

venously was less than 1.3 Gm (20 grains). Of nine patients treated intravenously six survived and when the attack was terminated the accompanying shock was relieved. The results are encouraging when compared with a series of 17 patients treated previously in 1931 when quinidine was not given by this method. Of the 17 patients 14 died within 15 days of the onset of coronary thrombosis. Of the three who survived two were patients with auricular fibrillation who developed ventricular tachycardia while taking quinidine for its control. The third patient developed ventricular tachycardia 46 days after the onset of coronary thrombosis. The abnormal mechanism disappeared after one dose of quinidine by mouth. These authors suggested mixing 4 Gm (60 grains) of quinidine sulfate in 500 cc (1 pint) of five per cent saline or glucose solution shaking vigorously, filtering and warming slightly. It was then given intravenously at the rate of 100 to 120 cc (3½ to 1 ounces) per hour.

Quinidine sulfate may prevent the onset of *ventricular fibrillation* in the intact heart of experimental animals. Levine²⁴ showed that ventricular fibrillation did not tend to occur when the faradic current was applied to the heart of the cat while under the influence of quinidine. This observation does not necessarily prove that the use of quinidine will prevent idiopathic rhythms in cardiac muscle in patients suffering from coronary thrombosis. In such patients previous defects in the conduction system and profound functional disturbances arising in the conduction system resulting from obstruction of the vessels may compel the ventricles to set up an independent rhythm at a low level in the Purkinje system if any cardiac activity is to be maintained. The action of the quinidine in therapeutic doses may cause auricular standstill or further increase any functional defect in the auriculoventricular conduction system leading to ventricular standstill. Schwartz and Jezer³⁴ studied two patients with auriculoventricular dissociation with transient seizures of ventricular fibrillation over a period of years. They found that when the ventricular rate was increased by quinidine ventricular premature beats appeared and these tended to appear in groups leading to attacks of ventricular fibrillation.

In the writer's clinic very few patients with ventricular tachycardia have been treated with quinidine. In these few the results have not been satisfactory. Only in those cases where there is great discomfort from

the tachycardia and where the patient has recovered somewhat from the commonly associated symptoms of coronary occlusion is the use of quinidine justifiable. The size of the dose required is so great and the changes in the cardiac muscle and conduction system so variable from hour to hour that the presence of the drug may be regretted before it can be eliminated from the body. Furthermore the paroxysmal and transient nature of the attacks make it difficult to draw conclusions as to the efficacy of the drug. It is likely that intravenous glucose and drugs like potassium may serve a more useful purpose in this type of arrhythmia.

VII REASONS FOR FAILURE

These are chiefly due to an improper selection of cases. When no better cardiac function can be hoped for with a regular auricular rhythm as in complete heart block the drug should not be used. In those patients with advancing myocardial disease and hypertrophied and dilated hearts or in those with late complications of valvular disease there is little chance of success and if this is accomplished the danger of accidents is so great as to contraindicate the drug. Some physicians have been too timid in the use of quinidine and have given inadequate doses. Others have failed because the drug was not kept up at frequent intervals day and night. An idiosyncrasy may result in failure or toxic symptoms or prolonged use may call a halt before adequate dosage has been given.

VIII TOXIC SYMPTOMS

These are not infrequent. They are essentially the same as those observed with quinine therapy. Buzzing in the ears, headache, vertigo, visual and mental disturbances are observed but from personal experience less frequently than from quinine. A number of patients have taken 0.12 or 0.2 Gm. (2 or 3 grains) of quinidine sulfate three or four times daily for weeks for annoying extrasystoles of auricular origin in the face of slight deafness which apparently was provoked by the action of the drug. The drug was so effective in giving relief from the palpitation that the patients chose to tolerate the deafness in preference to the symptoms caused by the arrhythmia. Anorexia, nausea, vomiting and diarrhea are commonly observed in those patients who receive large single doses and diarrhea may be troublesome when the drug is given over a long period of time. Along with these symptoms there may be abdominal pains of a spasmodic character. The *diarrhea* may be improved by the

use of a bland diet and bismuth or purgative if it is desirable to continue the drug. Rashes are described as with quinine. These may be urticarial, scarlatiniform or morbilliform in nature and are of a transient character. Petechiae may be noted occasionally when the heart becomes regular and may be associated with subacute bacterial endocarditis or the toxic action of the drug. Respiratory failure, dyspnea, precordial pain and attacks of syncope have been described but are not common. These attacks may be associated with arrhythmias, heart block or standstill which occur in these cases or may be on the basis of an embolus to the brain. Caffeine has been recommended as an antidote if collapse occurs.

A persistently rapid ventricular rate may be due to the local effects on the heart or to the action of the drug on the vagus. Jezer and Schwartz²¹ described a 1:1 flutter with an auricular rate of 200 per minute, followed by ventricular tachycardia and ocular toxic symptoms in a patient with auricular flutter who was treated with quinidine. In some cases the rapid ventricular rate or palpitation will make it advisable to discontinue treatment until after a course of digitalis. A persistently slow ventricular rate with auricular fibrillation or auricular flutter and a well defined block contraindicates the use of quinidine; an increasing block in the auriculoventricular conduction system while under treatment, should be a warning signal against further use of the drug. Campbell⁷ observed partial block after conversion of auricular fibrillation to normal rhythm. Extrasystoles, especially those arising in or below the auriculoventricular node, should warn the physician against the dangers of nodal or ventricular tachycardia which may terminate in ventricular fibrillation and death. Fischer¹³ noted bigemina during the administration of quinidine in a case of auricular flutter. A course of digitalis after an interval may make it possible to try quinidine again if much is to be gained by securing a regular rhythm.

Spiro and Newman³⁶ cautioned against further use of quinidine when the ventricular rate rose to 125 per minute or more. Auricular flutter may be noted during the transition period from auricular fibrillation to normal rhythm as observed by Warren.³⁷ Prolonged intra-ventricular conduction time and inverted T waves were danger signs. Boyer,⁴ Davis and Sprague¹⁰ and Wolff and White⁴³ warned against the dangers of auricular standstill during the intermediary stage when the rhythm became regular after auricular fibrillation. The possibility

of standstill of the whole heart was recognized as a cause of sudden death. Padilla and Cossio³¹ noted very marked local and general toxic symptoms after the intravenous method of administration. Pain was described along the vein and in the entire limb at the time of injection. Following this, there was frequently lassitude and drowsiness, pallor, chilliness, visual disturbances and nervousness (especially in women), vertigo, sensations of intense precordial pressure, with or without dyspnea, nausea, vomiting, and other disagreeable symptoms. It would seem that the dangers of thrombosis in the veins would be great with this method of injection and that local infiltrations and sloughing at the site of injection might follow any spilling of the solution into the tissues. The general symptoms reported are sufficient and of such frequency that this method should be adopted as a routine with hesitation.

IX. ACCIDENTS AND SUDDEN DEATHS

These have been numerous enough after quinidine to require special mention. They fall into three categories: (1) *Embolism*, resulting from the dislodgment of a fragment of thrombotic material on the auricular or ventricular wall, or on a valve, especially in subacute bacterial endocarditis, has been observed in a number of cases. The appearance of the embolism at the time when the normal rhythm is resumed in auricular fibrillation is so definite in a few cases that the relationship cannot be doubted. However, there have been several reports of control series which indicate that embolism is no more frequent in such cases than in those treated with digitalis or even without treatment. If patients to be treated are carefully selected and those with subacute bacterial endocarditis excluded, as well as those in whom the chambers of the heart are greatly dilated and where the action of the heart is poor, the dangers of embolism will be minimal. In patients with a previous history of embolism, a long time should elapse before quinidine is tried, or it should not be used at all.

(2) *Cardiac standstill* has been suggested by White and his co-workers as a probable cause of death in a few cases. If the auricular activity should cease during treatment and the ventricles also should be in such a state that independent rhythm could not be established, death would ensue. If care is taken not to use quinidine in patients who have well defined block in the conduction system, these accidents may be avoided.

Standstill of the heart may well be the commonest cause of sudden death in patients who are taking the drug as the following case notes will illustrate. Mrs J S 50 years of age had been under treatment for two years for congestive heart failure arising in association with paroxysmal auricular fibrillation. There had been a rheumatic mitral valvulitis of long standing with great enlargement of the heart and a relative tricuspid insufficiency. The discomfort occasioned by the abrupt onset of the attacks of auricular fibrillation was great and the symptoms associated with the simultaneous congestive failure which quickly supervened were so distressing that an attempt was made to terminate an attack which had persisted for two days by the use of quinidine. The drug was given in doses of 0.4 Gm (6 grains) every six hours day and night. On the second day after 2.4 Gm (36 grains) had been given without symptoms I was listening to the heart when there was a cessation of all cardiac sounds the patient suddenly relaxed became very pale and lapsed into unconsciousness. Within a few seconds which seemed hours slight cyanosis appeared and consciousness promptly returned as the cardiac sounds reappeared. Electrocardiograms taken soon thereafter showed an absence of auricular activity which previously and subsequently could be demonstrated. It must be assumed that either ventricular standstill or ventricular fibrillation precipitated the attack of syncope. Upon withholding the quinidine the auricular activity was resumed and digitalis was used.

(3) Ventricular extrasystoles may be the forerunners of the more serious complications of *ventricular tachycardia* and *ventricular fibrillation*. In those patients of advanced years with coronary vascular disease hypertension or intraventricular conduction defects quinidine if used should be given with great caution. Ventricular tachycardia arising in such cases is likely to be paroxysmal in nature and if the drug is at once stopped there is hope that they will cease as soon as the drug is eliminated from the body. Ventricular fibrillation may also be paroxysmal and in the same manner may promptly cease with recovery if the quinidine is withdrawn. The writer reported one such case in the early days of quinidine. These transient attacks were associated with attacks of syncope and cyanosis resembling Adams-Stokes syndrome. To show the possibility of quinidine acting in the opposite manner the case of Dock¹¹ is mentioned. He reported the case of a young man of 36 years who had had frequent attacks of syncope for 18 months. An electrocardiogram in a brief attack showed ventricular tachycardia or ventricular fibrillation rate 280 per minute. After an injection of adrenalin 0.3 cc (5 minims) of 1:1000 an attack was induced with a rate of 190 to 200

per minute. This patient was placed on quinidine sulfate 0.3 Gm (5 grains) three times a day and during the succeeding year had only one attack. This indicates the possible value of quinidine in spontaneous attacks of ventricular tachycardia or fibrillation as suggested by Levine and his co-workers. In a personal case of paroxysmal ventricular tachycardia in a young man quinidine was ineffective in controlling the attacks but excellent results were obtained with potassium salts.

SUMMARY

Wedd³⁰ has briefly summarized the prevailing opinions concerning the value of quinidine.

In conclusion from the pharmacologic standpoint quinidine is an ideal drug. It is readily obtained in a pure state inexpensive promptly absorbed from the stomach or it can be given parenterally its excretion is rapidly complete its powerful action can be measured quantitatively in animals and man and its high degree of effectiveness is combined with relatively low toxicity. But in therapeutics the use of this almost perfect drug is greatly restricted. It is indicated only in disorders of the cardiac mechanism occurring in reasonably sound hearts. And in this limited field the results are often disappointing not because of any fault on the part of the drug but because of the complexity of the mechanism that must be acted upon. However by judicious use every one may have a sufficient number of brilliant successes to make quinidine a worthy addition to the cardiologist's armamentarium.

In the writer's clinic a somewhat more optimistic view is taken at the same time recognizing the restrictions placed upon the use of this drug. The cases where the drug is indicated are carefully selected. It is given by mouth at frequent intervals in increasing doses until the desired effect has been obtained or until toxic symptoms make it necessary to discontinue its use. After the normal rhythm has been restored the drug is usually continued for an indefinite period in sufficient doses to maintain this rhythm or until the advancing underlying process calls for other drugs chiefly digitalis. In cases where the arrhythmia is transient and associated with infections thyroid disease or after operations the drug is only temporarily used.

In many cases quinidine is a valuable adjunct to digitalis therapy but in many cases replaces the latter as the drug of choice. It has been over a hundred years since digitalis was introduced into medical practice and it can safely be said that it is still improperly used by many physicians.

If the physician will apply what is already known about quinidine he will render a great service to that ever-increasing group of cardiac sufferers

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CHAPTER XL

TOTAL THYROIDECTOMY IN THE TREATMENT OF CHRONIC HEART DISEASE

By HERRMAN L. BLUMGART, M.D., and JOSEPH E. F. RISEMAN, M.D.

The present day treatment of congestive heart failure and angina pectoris offers much to prolong the comfort and useful life of patients suffering from these conditions. There frequently is a period in the lives of such patients, however, when medical measures are no longer adequate and the patients are forced to restrict their activities to such a marked degree that they become dependent on others for even the bare necessities of life and in many instances are confined to a bed and chair existence. The purpose and aim of total ablation of the normal thyroid gland is to enable some of these individuals to attain again a life of comfort and activity.

Experience has shown that complete removal of the normal thyroid gland is a valuable addition to the treatment of severe chronic heart disease. This method is not suited to all patients. It is a highly specialized procedure requiring great care in the selection of cases, preoperative preparation, operative technic and postoperative supervision. With proper attention to these matters, many patients with incapacitating chronic congestive failure, angina pectoris or cardiac asthma will attain a degree of comfort and activity which would otherwise be denied to them.

PHYSIOLOGY

Patients with heart disease experience discomfort when the damaged myocardium, valves or blood vessels are unable to maintain a circulation sufficient for the needs of the body. Treatment under such conditions is directed towards decreasing the needs of the body and at the same time improving the circulation. The value of rest in the treatment of heart disease is well known, the decrease in the metabolic needs of the body following total ablation of the thyroid relieves the heart of a considerable portion of its burden.

The work done by the heart is indicated by the cardiac output or the velocity of blood flow is considerably less in patients with myxedema than in individuals with normal metabolic requirements. Patients with myxedema suffer no symptoms from this slow circulation for the needs of the body are lessened to the same degree as the decrease in circulation. Following removal of the thyroid gland the needs of the body in patients with heart disease are decreased considerably as shown by a decrease in the oxygen requirements the work of the heart is lessened and a diminution or disappearance of the symptoms of circulatory inadequacy (congestive failure angina pectoris or cardiac asthma) occurs. Furthermore continuation of relief from overwork enables the heart to recuperate from the effects of prolonged excessive strain and permits the heart to *increase its reserve*.

Our knowledge of the interrelationship between the thyroid and heart disease dates back to the original description of thyrotoxicosis by Parry in 1825 when he described exacerbation of congestive failure with exacerbation of the signs of thyroid toxicity. The well recognized benefits conferred on thyrocardiac patients by subtotal thyroidectomy induced several investigators between 1919 and 1932 to remove part of the normal thyroid in patients suffering from nonthyrogenous heart disease but the results were unsatisfactory. Subtotal removal of the normal thyroid gland results in temporary lowering of the basal metabolism with coincidental temporary improvement of the symptoms of cardiac failure *total ablation of every vestige of thyroid tissue* is necessary to insure permanent hypometabolism with the resultant prolonged clinical improvement.

The relief from precordial discomfort and attacks of angina pectoris immediately following total thyroidectomy in some patients deserves special mention. It is evident from the numerous operations devised to interrupt painful sensations from the heart that cutting the cervical or thoracic sympathetic nerves at any one of a number of different points results in immediate but temporary disappearance of cardiac pain. Thus we find that cervical sympathectomy has been performed in at least eight different anatomical regions and that the thoracic sympathetic chain has been attacked in many different ways with relief from pain. Sympathetic nerve pathways in close association with the thyroid gland and its blood vessels have been demonstrated. Immediate relief from

precordial discomfort frequently ensues when the blood vessels to the thyroid gland are sectioned or the thyroid is removed from its bed. This relief is usually confined solely to that side of the body on which the operation has taken place and is usually of temporary (several weeks) duration.

It is unlikely that a decreased sensitivity to epinephrine is an important factor in the relief following total thyroidectomy. There is little evidence that the symptoms of congestive failure, cardiac asthma or angina pectoris are induced by either a hypersensitivity to epinephrine or an increase in circulating epinephrine. Furthermore, studies of the response to epinephrine injected intravenously before and after total thyroidectomy reveal no important differences.

RESULTS

The results of total thyroidectomy in more than 100 clinics throughout the world are now available. This comprises experience gained during the past six years in the treatment of more than 800 patients. A sufficient length of time has elapsed and a sufficient number of patients have been treated by total thyroidectomy to enable one to evaluate the results (Figs 1, 2, 3, 4).

It is evident that during the first year following the operation approximately one half to three-fourths of the patients are markedly improved in that they have either no recurrence of their symptoms or experience a marked decrease in the frequency and severity of symptoms despite physical activity greater than that possible before operation (Cases 1, 2, 3, 4). Another 10 to 15 per cent of patients although unable to increase their activity experience a definite decrease in the frequency and severity of attacks of angina pectoris, congestive failure or cardiac asthma.

A sizable proportion of those patients who show clinical improvement for more than one year after operation show continuation of marked improvement. This is evidently due to the fact that the underlying cardiac pathology is practically stationary and that the rest afforded the heart may lead in some of these cases to further definite clinical improvement. The operation does not alter the underlying cardiac pathology or the progressive nature of the disease; the mortality during the years following total thyroidectomy is high, therefore. It must be remembered that these patients had suffered from cardiac disability for months or years

Furthermore, many, especially those with arteriosclerotic heart disease, were more than 55 or 60 years of age at the time of operation (Case 1). Prognosis for such individuals is extremely uncertain, but the severity and duration of symptoms together with the advanced age suggest a short life expectancy. The impression cannot be escaped that the lives of

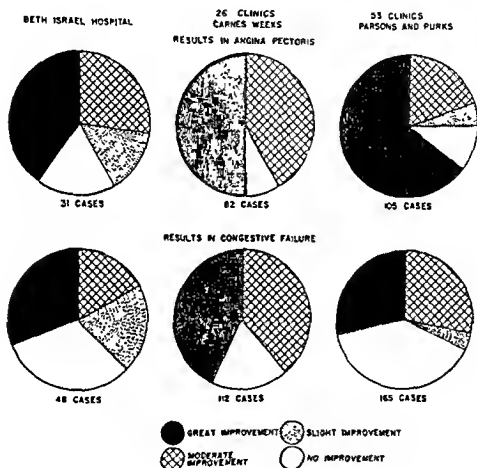


FIGURE 1. Results following total thyroidectomy at the Beth Israel Hospital and at other clinics

many of these individuals have been prolonged by total thyroidectomy. This is especially true in patients with congestive failure or cardiac asthma where the diminution of demands on the damaged myocardium has apparently interrupted a vicious cycle which in itself might have resulted in death without any progression of the underlying pathology.

The mortality in the years following operation is highest in patients with paroxysmal dyspnea and lowest in those with angina pectoris. The

mechanism of death is that usually observed in cardiac patients. Individuals with congestive failure die of embolic phenomena, subacute bacterial endocarditis, acute rheumatic fever or congestive failure. Patients with angina pectoris or cardiac asthma usually die of coronary thrombosis or left ventricular failure.

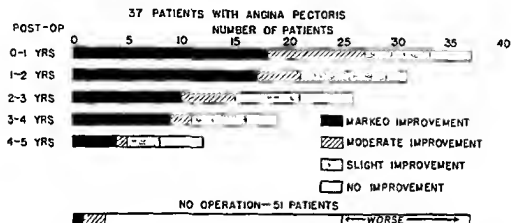


FIGURE 2 Results during the first five years following total thyroidectomy in 37 patients with angina pectoris compared with the results obtained in 51 similar patients who were not treated by operation

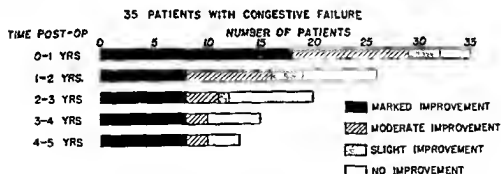


FIGURE 3 Results during the first five years following total thyroidectomy in 35 patients with congestive failure

Comparison of the results in congestive failure with those in angina pectoris and cardiac asthma. The results in congestive failure and those in angina pectoris or cardiac asthma are equally striking; differences are observed, however. The relief from cardiac pain is more spectacular for it becomes evident immediately after operation before the basal metabolism has become lowered. This "early relief" is due to interruption of afferent nerve impulses from the heart to the brain. It is usually temporary, for if the basal metabolism is maintained at the preoperative

level by thyroid administration angina usually returns within a few weeks. The more permanent relief of the pain is coincident with a drop in basal metabolism occurring during the weeks following total thyroidectomy.

Patients with angina pectoris are more likely to be able to undertake heavy physical exertion after operation than are those with congestive failure of cardiac asthma. This is to be expected for angina pectoris is an expression of localized ischemia whereas congestive failure is an expression of disability of the heart as a whole. The marked incapacity

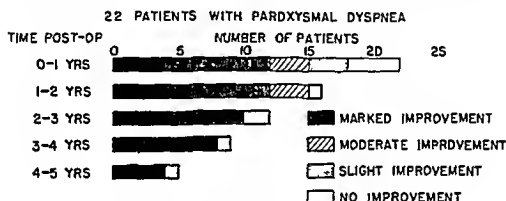


FIGURE 4 Results during the first five years following total thyroidectomy in 22 patients with paroxysmal dyspnea

of patients with congestive failure prior to operation makes results equally gratifying for although unable to undertake heavy physical labor these patients become able to care for themselves are no longer entirely dependent on others and are able to enjoy some of the pleasures of life which were previously denied them. Patients with cardiac asthma usually lose their symptoms immediately following operation and are free from attacks of paroxysmal dyspnea for months or years. Such patients however are usually unable to undertake any heavy physical labor because of the severity of the underlying condition.

COMPARISON WITH RESULTS OBTAINED BY OTHER METHODS OF TREATMENT

Thyroidectomy is best reserved for those patients who are incapacitated despite medical treatment. The fact that many of such patients lose their symptoms and regain an appreciable degree of activity following thyroidectomy is of considerable importance for there is little reason

to believe that further continuation of medical therapy alone would be attended by such striking improvement (Case 4).

The medical treatment of cardiac asthma is especially unsatisfactory. Few such individuals remain free from attacks following bed rest, digitalis, diuretics or intravenous glucose; in addition the life expectancy is rarely more than two years. Following total thyroidectomy approximately half such patients lose their attacks completely, many more are able to increase their physical activity considerably and approximately one fifth of the patients, despite their advanced years, are able to carry on for four to six years after operation (Case 3).

Medical treatment in congestive failure frequently yields satisfactory results. Thyroidectomy should be reserved for those individuals who are incapacitated despite medical therapy (Cases 2, 4). If 50 per cent of these individuals, otherwise doomed to a bed and chair existence, experience increased comfort, lose the signs and symptoms of congestive failure, are able to be up and about, wait on themselves and visit friends or the theater, the results may be considered worth while. Actually many of these patients are able to be economically self sustaining.

The numerous methods advanced for the treatment of angina pectoris bear witness to the inadequacy of medical therapy in many instances. Observation of patients who have refused operation or who because of low basal metabolisms were not treated surgically shows that few individuals under the usual methods of medical supervision regain the degree of relief obtained by operation. The mortality and frequency of coronary occlusion is approximately the same with both methods of treatment while progression of the severity of symptoms is probably more frequent in unoperated cases.

Alcohol injection of the upper thoracic sympathetic chain has many proponents. Freedom from severe and uncomfortable anginal pain is frequent following this procedure, however, White and White as well as others have commented on the distressing neuritic pain which frequently follows this simple operation; this neuritis may be constant, frequently persists for months and may be as distressing to the patient as the original angina pectoris. The exercise tolerance is not increased appreciably following alcohol injection; patients still experience discomfort on exertion but this is usually less troublesome, of a different character and in a different location than before injection. Total thyroidec-

tomy yields better results in patients with normal basal metabolic rates preoperatively alcohol injection is best reserved for those individuals with low basal metabolic rates or rapidly progressive disease

Our experience with denervation of the thyroid gland (according to the technic of Hargan and Lyon) in several patients has not been encouraging Disappearance of thoracic angina frequently results but pain in the arms or the jaws on exertion is rarely affected by this procedure furthermore the benefits are no more prolonged than by other methods which simply section sympathetic nerves Experience with the Beck or Shrugnessy technic of increasing the collateral circulation to the heart by anastomosing the myocardium with the chest wall or the omentum has not yet reached proportions necessary for confident evaluation The results to date appear promising but the operative hazards are great

A study of those patients who have not done well after total thyroidectomy reveals valuable information regarding the criteria for proper selection of candidates for the operation Such individuals can be divided into two groups—those in whom the results were never satisfactory and those individuals who showed definite improvement but who either died within a short time after operation or redeveloped their preoperative condition

Most patients who obtained no benefit from the operation had preoperative basal metabolic rates lower than minus 15 per cent Such individuals developed myxedema soon after operation without a further drop in metabolism sufficient to bestow adequate benefit others had so little cardiac reserve that it was impossible to keep them edema free even while under hospital supervision Still others were patients who were operated upon while suffering from an acute progression of the disease due to acute rheumatic fever or recent coronary occlusion

Several factors are responsible for the lack of prolonged maintenance of improvement in some cases The progressive nature of the underlying disease is of major importance Patients with cardiac failure due to malignant hypertension or syphilitic aortitis while relieved by the procedure and enabled to assume a more active life with marked diminution in symptoms have shown nevertheless a progressively downhill course Young patients with rheumatic heart disease may develop acute exacerbations of the rheumatic process which superimposed on the previous dam-

age results in recurrence of congestive failure. Similarly, patients with coronary arteriosclerosis may develop a fresh coronary occlusion with the attendant myocardial damage. It is as if the hands of the clock were turned back giving the patient a degree of comfort similar to that which they had enjoyed months previously but in the course of time the disease progresses so that symptoms again develop.

Inadequate postoperative supervision has been another cause for failure to maintain the benefits obtained during the first few months after operation. In several instances patients who travelled to other parts of the country were given large doses of thyroid. This was followed by return of symptoms and in some instances by death.

TECHNIC

Experience has shown that strict observance of certain details is essential in order to obtain satisfactory improvement in a maximum number of patients and at the same time assure a low operative mortality and absence of postoperative discomfort.

TABLE I

I SELECTION OF CASES

- 1 Stationary or slowly progressive course despite adequate medical therapy
- 2 Basal metabolism higher than minus 15 per cent
- 3 No contraindication to surgery (active infection, recent coronary occlusion, renal insufficiency, or failure to lose edema after adequate prolonged medical cure)

II PREOPERATIVE PREPARATION

- 1 Adequate use of rest, digitalis, diuretics, vasodilators, sedatives and if necessary oxygen in order to get patient edema free and in the best possible condition for operation
- 2 Test patient's sensitivity to any drug which may be used during or immediately following operation

III OPERATIVE TECHNIC

- 1 Minimum sedation before, during and after operation
- 2 Local anesthesia
- 3 Complete removal of every vestige of thyroid tissue
- 4 Avoid injury to recurrent laryngeal nerves
- 5 Preserve parathyroid tissue
- 6 Adequate fluids (1000 to 2000 cc) by mouth postoperatively
- 7 Careful observation for signs or symptoms of recurrent laryngeal nerve paralysis or parathyroid insufficiency

IV POSTOPERATIVE SUPERVISION

- 1 Frequent examinations
- 2 Continued bed rest until the basal metabolism falls at least 15 per cent
- 3 Increase activity gradually
- 4 Readjust digitalis dosage
- 5 Start thyroid therapy on first definite clinical evidence of hypothyroidism
- 6 Keep thyroid dosage as small as is consistent with comfort. If necessary to increase dosage do so by small increments

I Selection of Cases No individual should be considered for total thyroidectomy who has not had the benefit of adequate medical care including a period of complete bed rest. Patients who have not been on an adequate medical regime may respond satisfactorily to such supervision and may not need surgical intervention for months or years if at all (Case 5)

It is important to evaluate the rate of progress of the disease. The most beneficial results have been obtained in patients whose clinical course has been relatively stationary. Patients whose duration of cardiac symptoms is only a few months are not suitable candidates for they may well improve without operation or their course might be progressively downhill despite the procedure. Individuals with a recent exacerbation in symptoms are not suitable candidates for while the benefits may be striking during the early postoperative months as the disease process progresses these benefits will not be maintained. This is especially striking in patients with syphilitic heart disease malignant hypertension recent coronary occlusion or cases of active rheumatic infection.

A low basal metabolic rate prior to operation makes total thyroidectomy inadvisable. All the evidence to date indicates that the success of the procedure is related to a satisfactory lowering of the basal metabolic rate. Patients with a basal metabolism of minus 20 per cent or below usually develop myxedema soon after operation before the metabolism has been able to drop sufficiently to result in any relief of symptoms. In patients with a basal metabolic rate of approximately minus fifteen per cent careful clinical judgment is necessary in deciding whether the operation may be expected to yield favorable results. An elevated serum cholesterol or other clinical evidence suggesting mild hypothyroidism should weigh against operation whereas if these manifestations are absent and the

patient is nervous and hyperactive operation may afford considerable benefit

Operation is inadvisable in patients whose medical condition is due to an acute process such as active rheumatic infection or recent coronary occlusion such individuals frequently show striking improvement as the acute process subsides and furthermore are poor candidates for surgery of any sort

Terminal or extremely advanced cases should not be subjected to the procedure The drop in metabolic rate and its coincidental beneficial effect does not ensue for several weeks after operation If the probable duration of life will not permit this drop in metabolism operation should not be performed

II Preoperative Preparation Patients with chronic heart disease are notoriously poor risks for operative procedures Experience in many clinics has shown however that the operative mortality is less than five per cent if certain precautions are taken Most deaths occur in patients with congestive failure This emphasizes the necessity for removing all evidence of edema before undertaking operation The procedure is an elective one and the physician may take as much time as is necessary in order to make the patient's preoperative condition as favorable as possible In patients with congestive failure many weeks or months of complete bed rest and close medical supervision may be necessary in order to make them suitable candidates for operation (Case 2) Patients with angina pectoris similarly should receive a period of hospitalization before undertaking operation The occasional relief or disappearance of anginal attacks even in severe cases following hospitalization is well known (Case 5) In such individuals the mental relaxation brought about by hospitalization together with the relief obtained from vasodilators such as the more effective purines (theobromine sodium acetate) or small doses of nitroglycerin at hourly intervals minimizes the hazard of operation

It is of considerable importance to test the patient's sensitivity preoperatively to all drugs which may be needed after the operation A period of excitation following the use of a sedative may be a serious matter during the first 24 to 48 hours postoperatively Sensitivity to morphine is not infrequent in cardiac patients

III Operative Technic Postoperative complications particularly in patients with congestive failure are minimized if local anesthesia is used

and sedatives are administered as sparingly as is consistent with the comfort of the patient. With this regime patients are awake and raise accumulated bronchial secretion immediately after operation thereby reducing the danger of bronchopneumonia. Furthermore fluids can be administered orally thus avoiding venoclysis or hypodermoclysis. It is best to avoid all closed methods of anesthesia for these frequently tend to increase the amount of bronchial secretion and stasis even though given with high percentages of oxygen. In patients with angina pectoris nitroglycerin given at regular intervals throughout the operation is frequently of value.

The operation itself requires meticulous dissection. In order to insure the induction and maintenance of a low basal metabolic rate it is necessary to remove every vestige of thyroid tissue. This can be done as described by Berlin without injury to the recurrent laryngeal nerves or parathyroid glands.

Direct laryngoscopy after removal of one lobe of the thyroid is a valuable adjunct in preventing the possibility of bilateral vocal cord paralysis. The operation is terminated if there is any indication of injury to the nerve on the operated side and can be completed at a later date after sufficient time has elapsed to enable the nerve fibers to regenerate.

Close observation and adequate nursing care are needed during the first 48 to 72 hours after operation. The patient is given only sufficient sedatives for comfort. Narcosis is to be avoided. In contrast to the procedure frequently followed after subtotal thyroidectomy fluids are usually limited to 1500 cc. during the first 24 hours after operation. This can usually be taken orally by the patient. Continuous observation for signs of respiratory distress due to local edema or vocal cord paralysis is necessary.

Parathyroid tetany has not been encountered and parathyroid insufficiency has not been a troublesome complication. The glandules are readily recognized during the operation and can be preserved frequently with blood supply intact. A careful check should be made several times a day for signs of parathyroid insufficiency. This is usually evidenced earliest by hyperesthesia or a vague premonition on the part of the patient. Tests for Chvostek's or Trousseau's sign should be made several times daily. If necessary calcium chloride solution may be given orally. Injections of parathyroid extract are rarely needed.

IV Postoperative management and supervision is of extreme importance. During the first few months after operation when the thyroid dosage and physical activity must be adjusted accurately patients should be seen every two to four weeks. After the first year it is advisable to examine the patient at least once every three months.

Following total thyroidectomy the metabolism falls and remains at a low level. The distressing picture of cachexia strumipriva does not ensue however for as soon as the first definite clinical evidences of hypothyroidism supervene small doses of thyroid are administered daily. Experience has shown that the control of postoperative myxedema is feasible but requires close medical supervision. The aim is to maintain the basal metabolism at the lowest possible level compatible with comfort and at the same time to prevent the untoward effects of myxedema. Fatigue on exertion, sensitivity to cold, irritability or puffiness of the face are indications for thyroid therapy and unless treatment is given the basal metabolism will be lowered further, symptoms will progress and myxedema will develop at times suddenly in the course of a few days.

It is advisable in starting thyroid therapy to begin with 6 mg ($\frac{1}{10}$ grain) once daily. After one or two weeks trial it may be advisable to increase this dosage by adding 6 mg ($\frac{1}{10}$ grain) every day or every second day. The usual maintenance dose varies from 6 to 16 mg ($\frac{1}{10}$ to $\frac{1}{4}$ grain) (Armour's) once daily. Larger doses nullify the effects of the operation and since they cause return of the preoperative metabolic levels they may even be dangerous. Basal metabolic rates and at times serum cholesterol determinations are valuable in guiding therapy but only in relation to the clinical picture. In most instances a basal metabolism of minus 25 per cent to minus 30 per cent is maintained but this may vary in different patients from minus 15 per cent to minus 35 per cent. Experience has shown that such a low basal metabolism may be maintained for five or six years without any undue discomfort, progression of symptoms or decrease in the patient's ability to respond to thyroid.

It is important to remember that the underlying cardiac pathology has not been altered and it is therefore advisable to continue the restriction of activity until the patient has shown definite improvement. In cases with angina pectoris the early relief of pain may lead patients to resume activity early. This is to be avoided however, until the basal metabolism has fallen 15 per cent to 20 per cent at which time the de-

hands of the heart and the myocardial work will have been decreased. Patients with congestive failure are less likely to undertake undue physical exertion after operation. It is advisable in many cases however to continue bed rest for even longer periods than in angina pectoris in order to allow the heart to benefit by the lower metabolic rate and to recuperate from its former overtaxation. When the proper degree of improvement has become evident it is permissible to allow the patient out of bed under supervision and to increase activity slowly as the clinical condition warrants.

It is almost always advisable to continue digitalis after operation in patients with congestive failure. The dosage however frequently can be decreased slightly.

With the decrease in basal metabolism the heart may show some increase in size except in occasional cases of congestive failure where with the reestablishment of compensation there may be an initial decrease in the size of the heart shadow followed by a slight increase when lower metabolic levels are reached. The complexes in the electrocardiographic tracings become moderately reduced in amplitude especially at a low metabolic level. This is similar to the observations in spontaneous myxedema. These changes are not deleterious however for they are accompanied by an improvement in the cardiac condition as evidenced by the increased postoperative physical activity of the patient. Even when continued for a long period of time these changes are accompanied by no harmful effects. Many patients have shown such findings for three to five years without any decrease in their ability to undertake work and with no essential change in their response to thyroid.

SUMMARY

Experience during the past six years has shown that total thyroidectomy in the treatment of heart disease results in worthwhile improvement in 50 to 75 per cent of the patients. Following operation the basal metabolism drops and is maintained at a low level. Cachexia strumipriva does not ensue for small doses of thyroid are administered so as to keep the patient at as low a basal metabolic level as is compatible with comfort.

The treatment of chronic heart disease by total thyroidectomy is a specialized procedure which requires meticulous attention to details in order to obtain the maximum benefit. Operation is hazardous in these

cardiac invalids and will be accompanied by a high mortality and a high percentage of failures unless careful attention is paid to the selection of patients, medical management prior to operation, operative technic postoperative surgical care and the medical supervision throughout the remainder of the patient's life. Close cooperation between the surgeon and physician is essential. Not all patients are suitable for total thyroidectomy. A large number do well on medical care; others have a rapidly progressive course or are so ill that any operative procedure is inadvisable. There is a group of individuals who remain incapacitated and show little or no tendency to improve or become worse under adequate medical therapy. With proper attention to the details outlined above total thyroidectomy offers most of the patients operated upon a measure of comfort, activity and happiness which otherwise would be denied to them.

ILLUSTRATIVE CASES

CASE 1 Mr. G. O. B., a 65-year-old silk salesman, was referred from the Veterans Bureau for total thyroidectomy. Following typhoid at the age of 32, he developed fixation of the left knee; this prevented him from being active physically. He had had a chronic nonproductive cough for about 25 years.

For five years he had experienced daily attacks of spontaneous wheezing lasting 5 to 20 minutes; these frequently awakened him from sound slumber. During these five years he had slept more comfortably, using three or four pillows. For three years he had had swelling of the feet sufficiently severe at times to necessitate rest in bed. For four years he had experienced on walking a sensation like iron bands across the chest being turned by screws. On several episodes hypodermic medication was necessary in order to give him relief. He had had five hospital admissions for these symptoms during the three years preceding entry to the Beth Israel Hospital.

Physical examination revealed arteriosclerosis of the peripheral and retinal vessels. The blood pressure was 127/80. The liver was palpable two fingers breadth below the costal margin. There was no edema. His chest was emphysematous. The lungs were clear except for occasional rhonchi. The heart was of normal size by x-rays. The electrocardiogram showed low voltage in all three leads, left axis deviation and flat T₁. Examination of the blood and urine revealed no abnormalities. The basal metabolism was plus seven per cent.

Total thyroidectomy was performed by Dr. David D. Berlin on July 31, 1933. The postoperative course was uneventful. Within 24 hours he spontaneously volunteered the information that the bandlike constric-

tion which had been present intermittently every day during the past four years had not been present since operation. While in the hospital he found that he could sleep flat without dyspnea and could lie on his left side. He had no further attacks of asthma, no wheezing and no precordial pain. He was discharged on the eleventh postoperative day.

During the next two months he was seen once each week. At no time did he have any attacks of wheezing or pain. Two months after operation he tested himself by walking up a steep hill. He had no dyspnea but experienced mild pain between the shoulder blades. His weight increased from the preoperative level of 183 pounds to 200 pounds in spite of a low caloric diet. Five months after operation he returned to his work as a silk salesman. He noted no pain despite climbing stairs several times a day. About this time he complained of being somewhat irritable and had spells of the blues and a desperately depressed feeling. There were no external signs of myxedema. Thyroid 6 mg ($\frac{1}{40}$ grain) was prescribed. During the course of the next month this was adjusted so that he took 16 mg ($\frac{1}{4}$ grain) every other day. With this dose his irritability disappeared. After about six months of work he retired on a pension which he received for service in the Spanish American War. He spends his winters in Florida, the summers in Maine, coming to Boston for examination in the spring and fall.

Four years after operation he was admitted to the hospital for examination and reevaluation of his condition. The total diameter of his heart by x-rays was 14.7 cm. as compared to 13.4 before operation. The electrocardiogram showed delayed A-V conduction, P-R interval 0.24 second. He stated at this time that he had lost his asthma for about one year after the operation following which it had then returned but was much less severe, much less frequent and did not incapacitate him except for a period of several weeks around each New Year. The rest of the year he was up and about and quite active. For the first six months after operation he experienced slight pain between the shoulder blades on exertion but since that time he had had pain about once a year. He had had one attack while chopping wood, another while running up a hill to stop a dog fight, a third while trying to land a big fish in Florida. He experienced no symptoms of myxedema unless he omitted his daily thyroid in which case he felt irritable and drowsy. He required $\frac{1}{4}$ grain of thyroid daily except once every two weeks when he would take an extra $\frac{1}{40}$ grain for one day. The basal metabolic rate was minus 35 per cent.

Comment. This patient showed striking relief from angina pectoris following total thyroidectomy. He had been incapacitated and practically bedridden before operation but 41½ years later at the age of 70 he is physically and mentally active and free from pain except under unusual

physical and emotional activity This case illustrates the small doses of thyroid necessary to prevent the untoward effects of myxedema

CASE 2 Mr W D a 23 year old boy was first considered for total thyroidectomy in December 1932 at a hospital for the chronically ill Since the age of nine his activity has been restricted markedly because of heart disease He had been unable to attend school or to work except for occasional periods of a week or two when he tried to work as a bus boy Any exertion such as stair climbing made him much more short of breath than other children and also caused severe choking in the throat and an aching pain in the anterior chest radiating to the left shoulder A great portion of his life had been spent in hospitals For one year he had been living at a hospital for the chronically ill where he had been kept free of edema with great difficulty His activities during this period had been limited to sitting in a chair for several hours morning and afternoon the remainder of the time he spent in bed Whenever he was allowed to be up and about the ward for a few days generalized edema developed He had many hemoptyses He was believed to be too sick for any operative procedure Four months later his condition was unchanged and since there was no reason to expect further progress he was admitted to the Beth Israel Hospital for total thyroidectomy

Physical examination revealed the heart to be moderately enlarged with precordial bulging There were systolic and diastolic murmurs at the apex Blood pressure was 135/80 There was marked Cheyne Stokes respiration and fine rales at both bases but no demonstrable peripheral edema The cheeks lips and nose were cyanotic The electrocardiogram showed notching of the P waves right axis deviation delayed A V conduction (P R interval of 0.24) The basal metabolism was plus 5 per cent

Operation was performed on April 16 1933 He showed gradual but steady improvement during an otherwise uneventful convalescence Four months after discharge he was able to walk a total of approximately three miles a day without dyspnea

Six months after operation he complained of feeling tired all over and groggy He could not concentrate or remember things Basal metabolic rate was minus 35 per cent and there was slight puffiness of the face Thyroid therapy was started and after a period of adjustment was maintained at 6 mg ($\frac{1}{10}$ grain) a day Approximately one year after operation he began to work on a WPA sewing project and was able to be self sufficient for the first time in his life

Three and one half years after operation following excessive digitalis therapy he developed auricular fibrillation He has been observed several times a year during the 5½ years since operation but not once has he experienced congestive failure cardiac pain or hemoptysis He has been

working and self dependent and walks several miles during the course of the day

Comment: Despite constant medical supervision in a chronic hospital this young man was unable to remain out of bed for any considerable length of time. Although he failed to improve his condition after $1\frac{1}{2}$ years was no worse than when he first came to the hospital. It was reasonable to believe, therefore, that if the burden on his heart could be reduced, improvement would result and would be maintained, subsequent events have confirmed this. Surgery was not undertaken, however until he was freed completely of edema even though it required four months to do this.

The improvement following total thyroidectomy brought about new problems. He had been too ill from childhood to learn a trade or attend school, in fact, he owned no clothing save pyjamas and bathrobes. When these and related problems were solved he became an independent member of society.

CASE 3 Mr. L. M., a 53 year-old retired furniture salesman, was admitted to the Beth Israel Hospital on April 26, 1933. Seven and one half years previously, he was granted a life insurance policy at an increased premium because his heart was 'not normal'. Five years ago he lost his business and became depressed. His physician told him his heart was beating too rapidly and ordered him to bed for a period of ten days. He had had no cardiac symptoms until about one year ago when suddenly, while asleep, he was awakened and kept awake all night by a feeling of pressure in the middle of the chest, accompanied by difficulty in breathing and by choking in the throat. He felt too weak to go to work and remained in bed for ten days. During the year he experienced from 6 to 20 attacks of sudden dyspnea each week, these usually came at night while he was asleep. In addition he had a constant sense of pressure within the chest and about once a month he developed severe precordial pain lasting a few minutes. Bed rest was followed by temporary decrease in the number of attacks of nocturnal dyspnea but no change in the constant feeling of pressure within the chest. There had never been any swelling of the ankles.

Physical examination revealed moderate generalized arteriosclerosis and a moderately enlarged heart with a gallop rhythm. The blood pressure was 120/80. The lungs showed a few râles at the bases. The electrocardiogram showed left axis deviation intraventricular block, deep S_2 , low T waves in all leads and occasional ventricular premature beats. He remained in the hospital for about one week during which

period he was comparatively comfortable, although on several occasions during the day and night he would awaken because of shortness of breath. He was advised to return home under the supervision of his family physician and continue the same regime of bed rest, sedatives and digitalis. Three weeks later he returned, stating that he had had attacks of dyspnea every night during his stay at home.

Operation was performed by Dr. David D. Berlin on June 9, 1933. The postoperative course was uneventful except for an irritating cough and a rather uncomfortable feeling of pressure about the wound. Eleven days after operation he stated that he was aware of definite relief and a feeling of freedom from the pounding in his chest which he experienced before operation. He was entirely free from paroxysmal dyspnea or precordial pain.

During the next six months he was completely free from symptoms except for an increase in weight and some hoarseness and difficulty in speaking. He had increased his activity considerably against advice and four months after operation started working 10 to 15 hours a day as a furniture salesman moving heavy articles of furniture. Toward the end of the day he noted a little fatigue and slight shortness of breath but nothing compared to what he experienced before operation. An attempt was made to decrease his working hours but he stated he would rather die than go back to charity.

About six months after operation he complained of being drowsy, fidgety, restless and irritable. His face showed slight evidence of myxedema. There was no edema of the extremities. Thyroid 16 mg daily ($\frac{1}{4}$ grain), was prescribed. Following the administration of thyroid he noticed some dyspnea on exertion which disappeared when the thyroid was decreased to 16 mg ($\frac{1}{4}$ grain) twice a week. On examination five years after operation patient was still free from paroxysmal dyspnea. He experienced some dyspnea after walking approximately half a mile but this was not disturbing. His most distressing complaint was a salty taste in the mouth. The liver edge was barely palpable. Approximately one month later he again began to experience attacks of shortness of breath which came on suddenly at night about once every two to three days. These persisted for several minutes and then recurred three or four minutes later for a total of about 15 to 20 minutes. These were not as severe as those experienced prior to operation.

Comment. Medical care including hospitalization failed to free this patient of paroxysmal dyspnea. Total thyroidectomy, however, gave him relief for five years and enabled him to work and be self-sufficient during this time. Thyroid was not necessary for six months after operation and

as little as 32 mg ($1\frac{1}{2}$ grain) a week kept him free from the untoward effects of myxedema.

CASE 4 Mrs S R a 50 year old housewife had known of heart disease for 20 years. This was first observed three years after rheumatic fever. For seven years she had been troubled by marked swelling of the ankles and abdomen which despite treatment at home forced her to go to the hospital for about two weeks every six months. She had been receiving digitalis for 11 years and while not actually bedridden her activities had been restricted markedly for many years. Salyrgan injections together with ammonium chloride therapy had been given once or twice a week for five years. Following diuresis she would lose 12 to 13 pounds but would regain the weight at the rate of five to seven pounds in three days.

When examined she was very cyanotic and orthopneic. The heart was enlarged to percussion to both the left and the right and also in the region of the left auricle. There was a systolic thrill over the apex and a blowing systolic and diastolic murmur at the apex. The second pulmonic sound was accentuated. Rate and rhythm were grossly irregular. The blood pressure was 130/90. There was no evidence of peripheral arterio sclerosis. The lungs showed rales and a small amount of free fluid at both bases. The liver was palpable three fingers breadths below the costal margin. There was moderate pitting edema of the lower legs. Diagnoses of rheumatic heart disease, mitral stenosis and regurgitation with auricular fibrillation and congestive failure were made.

Studies of the urine showed no abnormalities. Red blood count was 7 000 000. Basal metabolic rate was minus 11 per cent. The electrocardiogram was normal.

Her admission weight was 130 pounds. Following injection of salyrgan her weight decreased to 123 pounds but on continued bed rest in the hospital with limitation of fluids and a salt poor diet she regained four pounds in five days.

On February 14 1934 total thyroidectomy was performed by Dr David D Berlin. As a prophylactic measure she was placed in an oxygen tent immediately after operation for two days. The postoperative course was uneventful. Her weight was maintained at 128 pounds. There was no evidence of fluid in the lungs abdomen or periphery. She was discharged one month after operation with instructions to remain in bed under the supervision of her doctor take digitalis 0.097 Gm ($1\frac{1}{2}$ grains) daily and thyroid extract 16 mg ($\frac{1}{4}$ grain) daily.

For the next year she continued to take salyrgan about once a week but was able to be up and about the house the greater part of the time. The liver was usually about two fingers breadths below the costal margin.

The extremities showed no edema. Basal metabolism was minus 20 to minus 30 per cent. After the first year she was able to be up and about the entire day, prepare the meals and do all the washing and cleaning for the household. She had no shortness of breath and no edema of the legs but required salyrgan about once every two months. Her therapy consists of thyroid 6 mg ($\frac{3}{10}$ grain) daily, occasionally alternating with 12 mg ($\frac{2}{10}$ grain) and digitalis 0.097 Gm ($\frac{1}{10}$ grains) daily.

Comment This patient with rheumatic heart disease, mitral stenosis and regurgitation and auricular fibrillation had had several hundred injections of salyrgan during many years but there had been little progression of symptoms. Total thyroidectomy has enabled her to undertake again her household duties and has cut down markedly the necessity for diuretics.

The amount of thyroid necessary to prevent myxedema is between 30 and 60 mg ($\frac{1}{2}$ and 1 grain) a week.

CASE 5 Mrs. B. L., a housewife aged 55, came to the Beth Israel Hospital on April 26, 1935, complaining of attacks of substernal pain during the preceding year which were precipitated by exertion and occurred as often as five or six times a day. There was no history of any prolonged attacks. The heart was just within normal limits by x-rays. The blood pressure was 180/80. Electrocardiographic tracings showed inverted T₁ and elevated ST₃. Basal metabolism was minus two per cent. Typical attacks of angina were induced by exertion under standardized conditions.

The clinical course of this patient was observed at weekly intervals during the next year. At least 25 different forms of therapy were tried without complete relief. On a régime of markedly limited activity (little housework, no shopping and very little walking out of doors) together with theobromine sodium acetate 0.5 Gm ($7\frac{1}{2}$ grains) and phenobarbital 30 mg ($\frac{1}{4}$ grain) four times a day, she was comparatively comfortable, having no more than one attack a day, but she was unable to do more without pain. Accordingly, she was referred to the hospital for total thyroidectomy.

During 23 days of hospital rest with the same medication, her attacks disappeared and it was decided to allow her return home for a further period of observation before undertaking operation. Since that time she has no more than one attack a week. Her activity has been restricted to work about the house with essentially no activity out of doors, but on the whole her condition is satisfactory and it does not seem as though operation were necessary.

Comment: This patient with angina pectoris was a suitable candidate for thyroidectomy in that she was incapacitated by angina pectoris despite medical therapy and her basal metabolism was normal. Following bed rest in the hospital, however, her symptoms have subsided so that although not free from angina she is sufficiently comfortable so as to make thyroidectomy seem unnecessary.

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CHAPTER XLI

HEART AND DEFICIENCY DISEASES

By SOMA WEISS M.D.

GENERAL CONSIDERATIONS

In certain nutritional states an intimate relationship exists between the disturbance of nutrition and the dysfunction of the heart and blood vessels. This is not surprising considering the sensitivity of the cardiovascular system to both extrinsic and intrinsic factors and the fact that in life one of the closest contacts of the body with environment comes through nourishment. Among the nutritional excesses increased intake of Calories and the resulting obesity is the only type which exerts a harmful effect on the heart and in particular on the circulation of man. There is no evidence that excess intake of vitamins is damaging to the cardiovascular system except in the case of *hypervitaminosis D* and even in that instance the deleterious effect on man has not been conclusively demonstrated. Deficiencies of nutrition on the other hand can affect the heart in several ways. To understand these cardiovascular dysfunctions certain general principles should be kept in mind. Thus in considering the interrelationship of nutritional deficiency and the cardiovascular system a clear distinction should be made between undernutrition and inanition, between water and salt deficiency on the one hand and specific vitamin deficiencies on the other hand. In general malnutrition due to the simultaneous and often proportionate reduction of *Caloric* intake vitamins and intermediary metabolic processes severe symptoms of vitamin deficiency are not apt to develop.

Intake of food substances rich in Calories but low in vitamin content while often associated with normal or even increased weight is the factor particularly predisposing to deficiency diseases. The specific type of vitamin deficiency in isolated form as observed in experimental animals is seldom seen in the clinic. Because man seldom chooses his food so that it lacks but one vitamin when we speak of a specific type of vitamin deficiency disease in the clinic we imply only that the deficiency of this

particular vitamin dominates the clinical picture. Usually, however, there is insufficient intake of several other vitamins. The clinical significance of combinations of several vitamin deficiencies is not known at present.

The average American diet of the indigent and low income group may be adequate in preventing frank deficiency diseases, but it is not an optimal diet, and does not supply a sufficient quantity of vitamins to create the necessary reserve. These suboptimal diets are often dangerously near to being grossly deficient. Judging from animal experimentation, a diet which is between the optimal and deficient levels may not cause classical symptomatic deficiency diseases, and yet may influence the development of growing organisms. This, in turn, may have an important influence on the ultimate power of resistance and on the longevity of individual organs as well as of individuals. Striking examples in the Orient demonstrate the development of "epidemic" beriberi in armies, consuming a diet containing a suboptimal amount of thiamin, after a prolonged march, or in populations stricken with malaria. In this country such examples have been observed during and after pneumonia, typhoid fever and other diseases.

It is essential to take cognizance of the fact that none of the clinical manifestations in any vitamin deficiency is specific. Anorexia, fatigue, night blindness, smooth tongue, neuritis, various skin lesions, cardiac dilatation, capillary fragility, edema, and changes in the bones and hair occur in a number of other diseases. As in other clinical problems, diagnosis of deficiency diseases requires a rational analysis of all available data. But with a detailed nutritional history, with the presence of a suggestive combination of symptoms and signs, and with the aid of appropriate chemical, physical, and therapeutic tests, the diagnosis of vitamin deficiencies rests on as firm a foundation as that for many other diseases.

One may divide deficiency diseases into two groups: (1) Those occurring in healthy subjects, (2) those developing in persons in whom intrinsic changes predispose to nutritional deficiencies even in the presence of a diet which is not grossly deficient. The first type of nutritional disturbance is a primary concern of public health; the second is mainly that of clinical medicine.

In addition to the composition of the diet, of primary importance are the absorption, rate of utilization, storage and elimination of vitamins.

These factors are greatly altered in a number of diseases. Thus various diseases of the gastrointestinal canal, liver, thyroid and pancreas in particular may play a conditioning or a precipitating role. Pregnancy, neoplastic and infectious diseases and conditions associated with increased metabolic rate in general also exert a modifying influence. Some of these diseases may preexist independently of nutritional deficiencies. In other instances, however, the nutritional deficiency causes functional or anatomical changes in the gastrointestinal tract and in other organs, and these in turn accentuate the predisposition, thereby creating a vicious circle. Often some of these conditioning factors are hidden, and this may be responsible for the clinical paradox that out of a group of persons consuming the same diet only some develop vitamin deficiency.

The finer mechanism of the individual symptoms of deficiency diseases must not be considered naively as arising from a simple lack of the specific nutritional substance in the tissues affected. Likewise, after the administration of vitamins, one should not expect miraculous changes. Practically all types of vitamin deficiency are accompanied by a series of changes in the intermediary metabolism which cause first biochemical lesions, later functional and finally structural alterations. These changes may progress from a state of easy reversibility to one of slow or nonreversibility. Certain of the deficiencies, particularly those of vitamin B and D, tend to be associated with structural changes of slow reversibility. Hence substitution therapy may or may not result in prompt and complete restoration of normal functions. Administration of vitamins will promptly cure chemical and physiological disturbances and will prevent further damage, but on the repair of severely damaged tissue vitamins may exert little or no effect. Such is the case in rickets, in polyneuritis and to a less extent in beriberi heart. These facts emphasize the importance of preventive rather than curative treatment. If a deficiency syndrome is present, active treatment is indicated. The oral administration of extracts and of food concentrates usually suffices, unless emergency or specific conditions exist. In preventive treatment, education of the public is important, and in this physicians must take the leading role.

GENERAL UNDERNUTRITION AND INANITION

Prolonged reduction of the Caloric content of the food produces significant changes within the cardiovascular system, as we have pointed

out.¹³ Fasting or severe restriction of diet results in bradycardia of 30 to 40 per minute, decreased arterial pressure, and a lowered metabolic rate. The lowering of metabolism in chronic undernutrition may be at times out of proportion to the loss of body weight. Since the blood flow is related to the level of oxygen consumption, presumably undernutrition is associated also with decreased blood flow and cardiac output. These changes may exert a beneficial effect in congestive circulatory failure caused by organic heart disease. It is probable that one of the factors involved in the beneficial therapeutic effect of the Carell diet is the cardiac effect of undernutrition. Recently, undernutrition of short duration has been found useful in the treatment of heart failure including that originating in coronary thrombosis.^{4, 5} On the other hand, prolonged undernutrition, causes unfavorable changes in the cardiovascular system, and chronic undernutrition causes wasting not only of the skeletal muscles, but also of the myocardium. It has been shown that in both adult animals and man the myocardium may lose 20 to 50 per cent of its average normal weight due to chronic undernutrition. As a rule the myocardium of young animals and children is more resistant to loss of weight so induced.

The clinical significance of malnutrition in relation to function is not adequately understood at present, because detailed studies with exact measurements are not available. However, clinical experience indicates that populations afflicted by famine are poor surgical risks. We have had ample opportunity to observe that poorly nourished cats and dogs are apt to respond to surgical procedures with sudden cardiac standstill. That this type of death can be prevented by preoperative nourishment of these animals makes clear the clinical implication that before surgical operation of choice is performed malnourished persons should receive for weeks, if possible, a well-balanced diet.

Among the calorigenic food substances, deficiency of proteins and carbohydrates can at times have a special bearing on dysfunction of the heart and of the circulation in general. The effect of blood protein in the maintenance of the osmotic pressure of blood is well known. If the protein content of the food is low over a long period, or if the protein formation is seriously disturbed, the blood protein may reach a level which predisposes to the formation of edema. This effect of hypoproteinemia is particularly important so far as the pulmonary circulation is

concerned. We have pointed out that patients with tendency to left ventricular failure are more inclined to develop pulmonary edema than those with normal protein content. Hypoproteinemia in presence of heart failure increases the tendency to dyspnea and orthopnea. Chronic protein deficiency like that occurring during famines can result in generalized edema (nutritional edema) which exerts a harmful effect on the heart and circulation particularly if it involves the lungs. If the serum protein is low there is loss of fluids into the tissues and a tendency to circulatory collapse may also develop. If pleural exudates or transudates in various organic diseases require repeated taps it is essential for the patients to consume high protein diet to prevent severe hypoproteinemia.

Sudden reduction of the level of the *blood sugar* can result in attacks of syncope, circulatory collapse and convulsions at times associated with a sharp reduction of the arterial pressure. Such acute circulatory changes develop as a result of spontaneous or induced *hyperinsulinism*. Rarely a similar type of circulatory collapse may develop in diabetic patients whose blood sugar has been lowered too abruptly from an unusually high level. Hypoglycemic shock in elderly persons particularly those with coronary sclerosis may be accompanied by paroxysmal cardiac irregularities and rarely by angina pectoris. Administration of glucose promptly abolishes these attacks. In patients with neoplastic growth of the pancreas or of the other glands of internal secretion surgical removal of the tumor prevents further attacks.

WATER AND SALT DEFICIENCY

It is significant that while the human body possesses adequate mechanisms for the maintenance of a homeostatic state despite increase in the water and salt intake its protective mechanism against loss of water and salt proves frequently to be inadequate. The loss of the water and salt content of the body can lead rapidly to hemoconcentration and this in turn to circulatory collapse. Physicians were slow to appreciate the fact that the high infant mortality from diarrheal states and the decimating effects of cholera and other dehydrating infectious diseases on certain sections of the human race are caused *primarily* by loss of water and salt and that simply by supplying adequate water and salt these high mortality rates can be abolished or at least diminished. The ease with which per

sistent diarrhea leads to dehydration and circulatory collapse becomes understood if one recalls that normally between 7500 and 10,000 cc. of fluid are secreted into the gastrointestinal canal within 24 hours. In the healthy person this fluid is reabsorbed to a large extent. In patients with vomiting and diarrhea the loss of a large portion of this intestinal fluid must be corrected or there develops a tendency to reduced blood volume, hemoconcentration and shock. It is not clearly established at present whether in this type of collapse and shock there is also some cardiac dysfunction. The primary disturbance in circulatory collapse is the diminished return of blood and not the damage to the heart. Theoretically, nevertheless, there is the possibility that anoxia resulting from the reduced cardiac output, the dehydration and accumulation of toxic waste products can exert a harmful effect on the myocardium, as also evidenced by reports indicating that animals dying from thirst can lose 30 to 40 per cent or more of their cardiac weight. It is known also that any type of circulatory collapse can precipitate minor or major thrombosis of the coronary arteries particularly in presence of coronary sclerosis.

It is evident, therefore, that in diseases with long persisting fever with fistulous opening, as for example biliary or pleural fistulas, with heat exhaustion, with adrenal insufficiency, or with vomiting in pyloric stenosis, an adequate supply of water and salts is most effective in preventing peripheral failure of the circulation. Rarely circulatory collapse and shock due to dehydration and hypochloremia may result also from the indiscriminate use of gastric or duodenal drainage with suction ("Wangenstein tube"). We have observed patients in whom collapse developed as the result of such removal of a large amount of intestinal fluid. It is essential that fluids and salts should be replaced rectally or parenterally in these patients.

DEFICIENCY OF CERTAIN NUTRITIONAL FACTORS IN PERNICIOUS ANEMIA

Deficiency of iron and of certain other nutritional factors essential to blood formation produces through various types of anemias changes in the heart and the peripheral circulation. The heart in anemia has been discussed in Chapter X. Although a statistical correlation exists between the severity of the anemia and the degree of cardiac dilatation, many individual exceptions exist. The cardiac disturbances observed in patients with anemia do not depend solely, however, on the increased

cardiac work as a result of elevated cardiac output for frequently the anemia is associated with other nutritional deficiencies. This observation is also attested by the fact that in these patients the return of normal hemoglobin level is not followed by disappearance of the cardiac size, the gallop rhythm or other manifestation of cardiac dysfunction. Only after the general nutritional state has been improved will the heart become normal.

In pernicious anemia fatty degeneration of the myocardium accentuated around the venous ends of the capillaries can result in the tiger lily appearance of the cut section. This picture was relatively frequent in pernicious anemia before the introduction of liver therapy but has since become rare. In pernicious anemia the cardiac symptoms and signs are the same as those in severe secondary anemias. Palpitation, dyspnea and syncope are the commonest complaints. Dilatation of the heart develops usually first to the left and then to the right. The shape of the heart is often globular. Systolic murmur of varying intensity may appear followed by gallop rhythm. If the anemia reaches a level below 20 per cent of hemoglobin, short diastolic murmurs over the base and less frequently over the apex may appear. As the patient improves the physical signs disappear in reverse order. The hemodynamics of the circulation in pernicious anemia is similar to that in secondary anemias. The cardiac output and the velocity of blood flow is increased and the peripheral utilization of oxygen is small. In severe pernicious anemia observations taken immediately after exercise record the oxygen of the venous blood as low as one or one half volume per cent. The dyspnea in pernicious anemia can be surprisingly slight even when the degree of anemia is severe. I have observed patients with hemoglobin levels of 18 per cent and 14 per cent respectively who walked slowly without difficulty on the level. The degree of dyspnea at the same hemoglobin level depends on the time element of the development of the anemia. A rapidly developing anemia is more apt to be associated with dyspnea. When the hemoglobin level reaches the unusually low level of 10 to 12 per cent the patient may still feel fairly comfortable if immobile and in horizontal position but on moving or sitting up there is tendency to dyspnea and to attacks of syncope. This syncope is usually vasovagal in type. Patients with severe anemia and cardiac symptoms and signs experience little or no orthopnea or signs of pulmonary congestion.

although there is a tendency to develop bronchopneumonia. Potent liver extract should be administered in large doses in cases of pernicious anemia with cardiovascular disturbances. A remission may be precipitated as soon as 24 to 48 hours. In patients with severe anemia, however, emergency transfusions are indicated. Blood should be infused very slowly, and a constant watch should be kept for indications of cardiac embarrassment, evidenced by increased dyspnea, pulmonary congestion and edema, and increase in the venous pressure. In addition to the liver extracts patients should be given a highly nutritious diet.

BERIBERI

For a long time beriberi has been considered a disease of the tropics and the Orient. Only recently it has been discovered that this disease in its various forms occurs not only in this country but also in the other Occidental countries. Recent advances in the study of nutritional deficiencies make clear the rationale of the long-established clinical observation that patients suffering from beriberi are not necessarily malnourished; at times, indeed, they are obese. While in certain parts of the world the incidence of beriberi is high, it is less so in this country. Until recently the etiology of beriberi has been obscure, and infectious, toxic and climatic factors have been considered in its etiology. Gradually, however, more and more evidence has been accumulated pointing to nutritional origin. While in patients with beriberi the nutritional disturbances are usually multiple, substantial evidence is available that the primary etiological factor is thiamin deficiency. With the recognition of the nutritional origin of beriberi and with the practice of preventive medicine, the frequency of beriberi has been reduced even in the Orient. Thus Wenckebach reports that in Java with a population of 45 million people large epidemics of beriberi exist no more.¹⁴

In both the Orient and Occident beriberi may be classified as one of three main types: (1) The *neuritic* or "dry" beriberi with symptoms and signs related to the nervous system. (2) The *edematous* or "wet" type in which the clinical picture consists mainly of diffuse dependent and nondependent edema. This edema in its distribution is not unlike that observed in glomerulonephritis or in toxemias of pregnancy. Fluid may appear in the serous cavities including the pericardial sac. (3) The *cardiac* type which varies in severity and which is discussed here.

Frequently beriberi appears as a combination of two or of all three forms. Since the presence of a pronounced degree of polyneuritis in beriberi protects the heart, the cardiac symptoms in these cases are usually absent or mild, whereas in persons without polyneuritis or with mild manifestations who perform severe muscular work, a severe type of congestive failure of the circulation is prone to develop.

It is known that the thiamin requirement of the body is proportionate to the Caloric intake or more precisely to the metabolic rate of the body. For this reason a diet such as the polished rice of the Orient and the alcohol of the Occident which is rich in Calories but poor in thiamin predisposes to beriberi. It has been estimated that while the average American diet is considerably poorer in its thiamin content than it was a century ago, it still provides us with a 20 to 80 per cent margin of safety. However as indicated by various estimates and analyses of diet, there must either be a relatively large number of people who consume a diet below this margin of safety, or the diet consumed becomes inadequate under hard physical work or under the elevated body metabolism resulting from pregnancy, infectious and metabolic diseases, or surgical procedures. In other diseases, particularly in certain ones of the gastrointestinal tract, the intake of thiamin may be above the critical level, but there is poor utilization and absorption of this and other vitamins. Under these circumstances a subclinical or presymptomatic thiamin deficiency can change to a typical case of beriberi, or a mild form of the disease can change to a severe type. It is characteristic of beriberi with cardiovascular disturbances that the heart and vascular systems are very susceptible to trauma and infections, and that there is constant danger of circulatory collapse, acute pulmonary edema, and fatal bronchopneumonia. The term "beriberi heart" is not entirely appropriate because in addition to the heart, the peripheral vascular system is also likely to be damaged.

The *symptoms and signs* of beriberi with cardiovascular disturbances vary considerably with the severity of the disease. The patient is prone to be a young or middle-aged adult who develops fatigue, palpitation, and the sensation of rapid heart action. There may be a sensation of pressure over the upper part of the abdomen. Pain over the calf muscles and paresthesias over the lower extremities are frequently present. Varying degree of dyspnea and swelling of the body is a usual complaint of patients suffering from the severe type of the disease. Cough, orthopnea,

and paroxysmal dyspnea (cardiac asthma) are further manifestations of the condition. In some instances, attacks of dyspnea appear with unexpected suddenness in persons who have been in vigorous health.

On examination the patient may appear comfortable or may be in great distress caused by the severe dyspnea and orthopnea. Often they are nervous, anxious and restless. The eyes may be shiny and slightly prominent. Edema may be absent, slight or generalized, and frequently is hard to nondependent and so evenly distributed that the patient may appear robust until the loss of 30 or 40 pounds of fluid reveals that generalized water retention has been present. Thus a patient with full, round face and robust appearance can change within a week after the start of treatment to a thin faced person with a delicate bodily structure. The color of the face and mucous membranes is usually normal, although with severe pulmonary congestion and edema, cyanosis may be present. The skin as a rule is warm. At times the presenting clinical picture is a combination of congestive failure of the circulation and peripheral collapse and shock.

The heart in beriberi is not always enlarged. We observed patients suffering from the disease who had evidence of cardiac disturbances and electrocardiographic changes but in whom the size of the heart on x ray examination was normal. Because of the forceful heart action, there may be extensive thoracic pulsations, falsely suggesting cardiac enlargement. In severe beriberi, however, there is usually enlargement to both right and left. The heart rate is usually rapid with prominent precordial pulsation. On palpation there is evidence of forceful cardiac impulse and coarse vibratory movements which are not thrills. Gallop rhythms, pre-systolic and protodiastolic in type, are prone to be present. In severe cases, murmurs may appear *characterized chiefly by rapid changeability*. They may be present in the morning but absent in the afternoon, and they become accentuated after exercise but rapidly decrease in intensity after rest. The usual murmur is a loud and late short or somewhat diffuse systolic one, although occasionally diastolic murmurs may also appear, in which case a false diagnosis of valvular heart disease may be made, only to find that the murmurs may be absent the next day.

The peripheral arterial pulsations are normal in mild cases and prominent in severe ones. As in anemias, sepsis and thyrotoxicosis, the pulse can be high, bounding, and unusually soft, with pistol sounds over

the carotid and femoral and less frequently over the brachial arteries. The veins are often distended and the pressure elevated. The arterial pressure is either normal or characterized by a moderate elevation of the systolic pressure. Moist rales and signs of fluid in the pleura, pericardium and peritoneum occur in severe cases. The liver can be acutely enlarged and tender.

Edema varies in degree and is not always present. The edema cannot be attributed primarily to decrease in the osmotic pressure of the blood even when that is present for the edema often disappears while the osmotic pressure remains essentially unchanged. The protein content of the edema fluid is low. In many respects the edema is like that in glomerulonephritis and in toxemia of pregnancy.

Wenckebach and other observers have emphasized the fact that in untreated cases particularly in slender persons the calf muscles are enlarged and hard. This swelling of the muscles is independent of subcutaneous edema or manifestations of neuritis. As a result the patient experiences pain and difficulty in walking. I have seen hardening and swelling of the muscles of the shoulder and arm also in severe cases of Occidental beriberi. With rest and treatment the swelling disappears rapidly.

In a group of seven patients attacks of *syncope* were observed which were associated with asystole and fall in the arterial pressure and which could be induced by stimulation of the carotid sinus. The hyperactive reflex in these patients is of the vagotonic type. It is of interest that long before we recognized beriberi with cardiovascular manifestations in this country we described the occurrence of this type of syncope in patients with nutritional disorders and demonstrated that the hyperactivity of this carotid sinus reflex subsides after administration of a vitamin rich diet.

Circulatory collapse may be preceded by congestive failure of the circulation while in other instances it occurs with tachycardia as the only premonitory sign.

Patients with cardiovascular manifestations of beriberi particularly congestive failure of the circulation are prone to develop *fever*, the cause of which often remains obscure although in some instances it is referable to bronchopneumonia. The condition of these patients often becomes much more serious with the onset of an elevated temperature.

and in some cases observed by us the fever seemed to have precipitated the congestive failure.

In addition to these specific manifestations of cardiovascular beriberi polyneuritis and symptoms of other nutritional deficiencies are often present. Pellagra and beriberi are prone to be present simultaneously and occasionally scurvy and beriberi coexist. The occurrence of psychosis, glossitis, constipation or diarrhea, dermatitis, anemia, optic neuritis, dysphagia, aphonia, spooned nails and purpura in addition to cardiovascular manifestations tends to confirm the existence of beriberi. In Occidental alcoholic beriberi cirrhosis of the liver is often present.

Electrocardiographic Changes The electrocardiogram in beriberi often shows depression or inversion of the T waves similar to that observed in myocardial disease. The electrical systole (Q-T interval) may be prolonged. Auricular and ventricular premature beats and more rarely auricular fibrillation and intraventricular block may develop. These electrocardiographic changes disappear after treatment with varying rapidity. In some of the cases studied the electrocardiogram did not return to normal until weeks after other signs of improvement.

Hemodynamics of the Circulation The clinical manifestations of beriberi suggests a state of the circulation which is a peculiar combination of overactivity and failure of the heart. It is not unlike that observed in thyrotoxicosis or in rare instances in large arteriovenous fistulas. Measurements of the circulation confirm such a clinical interpretation of the circulation in beriberi. The vital capacity of the lungs is low. The velocity and volume of blood flow is absolutely or relatively increased. The utilization of oxygen in the extremities is small. Failure of the circulation in beriberi depends on the combined effects of dilatation of the peripheral arteriolar system and impaired myocardial function. As a result of dilated arterioles the return of the blood to the right ventricle is increased making the right sided type of failure relatively common while left ventricular failure occurs in a smaller group of patients. Wenckebach noted that administration of epinephrine the effect of which is like that of sudden muscular exertion or infection usually accentuates the symptoms and signs of the cardiovascular disturbances while pitressin improves them. Following the administration of thiamin the changes in the hemodynamics subside.

Chemical Changes Hypoproteinemia either slight or pronounced is usually present. In severe cases with oliguria the nonprotein nitrogen content of the blood is apt to be moderately elevated. In some instances the fasting blood sugar and lactic acid are moderately high and slight glycosuria is present. In severe cases of Oriental beriberi the blood pyruvic acid is high but although we observed high bisulfite binding substances no pronounced elevation of the blood pyruvic acid was observed in the Occidental cases.

Morphological Changes The weight of the heart is normal or increased. Cardiac hypertrophy is prone to develop in chronic deficiency. The ventricles particularly the right are frequently dilated. In histologic examination the myocardium may appear normal or there may be interstitial edema and hydropic degeneration of the myocardial fibers. The degree of severity in these changes varies and our studies indicate that they are not specific to beriberi but can occur in other diseases of the heart. The so-called interstitial edema probably represents collagenous material since the water content of the myocardium in these cases remains normal. The variation in the structural changes in beriberi offers inadequate explanation for the variation in the onset of response to treatment as observed in the clinic.

Pathogenesis Although as indicated above multiple nutritional abnormalities play causative roles in the development of beriberi with cardiovascular manifestations the following evidence indicates that thiamin deficiency is the primary factor: (1) The thiamin content of the diet of these patients is particularly low while the Caloric intake is relatively or absolutely high. (2) Recent chemical investigation has revealed that the thiamin excretion in the urine in these cases is low.⁶ (3) Administration of thiamin causes improvement and disappearance of the symptoms of the disease. (4) If healthy persons are kept on a diet lacking thiamin electrocardiographic changes similar to those observed in beriberi are induced.¹⁵ (5) Animals kept on thiamin deficient diet develop electrocardiographic changes similar to those observed in man¹¹ and under certain experimental conditions congestive failure has been induced in pigeons and dogs.¹⁰ On post mortem examination hydropericardium, pulmonary edema and congestion of the lungs and liver are present in these animals. In a large group of these thiamin deficient animals the heart showed dilatation of the right auricle and ventricle. Focal

necrosis intercellular edema and vacuolization of the myocardial fibers as well as of some of the conductor and ganglionic fibers were observed. Thus the morphological changes in the thiamin deficient animals were similar to those observed in beriberi.⁶ If thiamin-deficient animals with electrocardiographic changes and congestive failure received thiamin recovery followed promptly. Thus the clinical and experimental evidence now available provides proof that beriberi so far as the cardiovascular manifestations are concerned is related to thiamin deficiency.

The Role of Alcohol Excessive intake of alcohol often precedes the development of beriberi in the Occident. For this reason polyneuritis which follows the use of alcohol has been attributed to its toxic effect. The concept that the thiamin deficiency connected with the use of alcohol rather than the alcohol *per se* is the causative agent can be supported by the following evidence accumulated in recent years: (a) The clinical manifestations of alcoholic beriberi are identical with those of the non-alcoholic type. (b) Both types usually respond favorably to thiamin. (c) Chronic alcoholism is common while beriberi is rare. (d) Pharmacologic studies fail to indicate that pure alcohol without thiamin deficiency causes cardiovascular damage or polyneuritis. (e) Administration of alcohol and thiamin or vitamin B concentrate improves the clinical manifestations of alcoholic beriberi. (f) Chronic alcoholism is apt to be associated with other manifestations of vitamin deficiency such as night blindness, scurvy and pellagra.

It is possible however that alcohol and other nutritional factors play a secondary predisposing role just as a pure carbohydrate diet predisposes to beriberi. Thus it has been shown experimentally that if vitamin B deficient pigeons are fed fatty acids instead of carbohydrates muscular cramps characteristic of the deficiency do not develop.

Alcoholic beriberi is prone to develop among persons drinking hard liquors such as gin or whiskey but it can develop also among heavy beer drinkers. The vitamin B content of the American beer is low. Beriberi has not been observed among wine drinkers. Other conditions predisposing to beriberi in the Occident are infectious diseases among persons living on a suboptimal intake of thiamin, peptic ulcer in patients consuming an unbalanced diet, disturbances of the gastrointestinal tract associated with diarrhea or with surgical trauma, thyrotoxicosis particularly associated with gastrointestinal disturbances, diabetes and the cup

rices of food cranks who consume high carbohydrate diet with an insufficient amount of vitamins. Because not all patients subject to the same malnourishment develop beriberi it is probable that in addition to the diet certain intrinsic bodily factors are operative in the pathogenesis of this deficiency. Just as it is not understood at present why in pernicious anemia some patients are affected chiefly by the anemia and others by anemia cord lesions so in beriberi it is obscure why some patients predispose to cardiovascular dysfunctions and others to polyneuritis.

In Japan and in the Philippines beriberi occurs in infants. This type of beriberi develops mainly among breast fed rather than artificially fed babies which suggests that beriberi and vitaminosis in the mother can have an important bearing on the nutritional state not only of the newborn but also of the nursing infant. Whether some instances of idiopathic cardiac hypertrophy will be explained on this basis cannot now be stated and this problem has not been adequately investigated in the United States although Hays² reported the occurrence of beriberi in infants who suffered from celiac disease.

Differential Diagnosis. We have pointed out elsewhere¹⁰ that as indicated by recent reports beriberi with cardiovascular manifestations occurs in various countries in the Americas and Europe. Fundamental differences between the Oriental and Occidental beriberi do not exist although obviously in the large epidemics of Oriental beriberi the severe form of the disease is commoner than that in the Occident. The cardiovascular disturbances in beriberi in our experience do not form a rigid clinical syndrome but more recent reports from the Orient indicate that there too beriberi occurs with clinical manifestations of both right and left sided failure.

The question may well be raised as to the existence and clinical interpretation of beriberi in the Occident prior to the recent discovery of its occurrence and its relation to thiamin deficiency. We have discussed the evidence indicating that this type of heart disease has been observed from time to time in the past but has been interpreted as alcoholic myocarditis, obscure myocarditis, arteriosclerotic heart disease and the like.¹⁰ The suspicion that the disease might be beriberi or that it had some similarity to beriberi has been raised however in the past. For example so keen a physician as Graham Steele remarked in 1906 of the clinical characteristics of dropsy: "Capricious distribution of

dropsy is specially apt to occur in cases of the cardiac muscle failure of beer drinkers and of the disease known as beriberi of both of which diseases it is curious to note peripheral neuritis is a clinical feature.

In the diagnosis of beriberi it is essential to appreciate the fact that the individual clinical characteristics of the cardiovascular changes just as in other cardiovascular diseases are not specific. Nevertheless the combination of the clinical manifestations lack of etiology of other types of heart disease and history of unbalanced diet permit a diagnosis with a fair degree of probability. The combined pressure of congestive failure of the circulation and a relatively or absolutely increased rate of the circulation rules out several other types of heart failure. The simultaneous presence of other manifestations of nutritional deficiency disease particularly polyneuritis gastrointestinal disturbances pellagroid skin lesions and a tendency to psychosis make the diagnosis probable. With the recent development of chemical methods for the quantitative estimation of minute amounts of thiamin it is expected that eventually measurements of the blood thiamin and the excretion of the thiamin in the urine will be of great aid in the more exact diagnosis of beriberi.

It should be remembered that not every obscure myocardial failure without valvular disease or without histological changes in the myocardium is a beriberi heart. In recent years while attempting to select cases of beriberi with heart disease we have been impressed by the relative frequency of other types of heart disease which like beriberi heart are not as yet commonly recognized by physicians. Beriberi with heart disease should be differentiated from diseases of the heart associated with arteriovenous aneurysms thoracic and spinal deformities rare cases of cirrhosis of the liver amyloidosis and xanthomatosis glycogen disease (Van Gierke) pituitary and ovarian disease glomerulonephritis idiopathic postpartum myocardial failure lupus erythematosus disseminatus scleroderma Boeck's sarcoid pericarditis nodosa thromboangitis obliterans certain respiratory infections trichinosis progressive muscular dystrophy and Friedreich's ataxia. The specific characteristics of these diseases of the heart have been described elsewhere.)

Organic Heart Disease and Beriberi Because patients with organic heart disease often consume inadequate or unbalanced diet nutritional deficiencies can be expected to occur in these persons. In the majority of instances however we are dealing with a low Caloric diet rather

than with a diet favorable to the induction of beriberi. Until the chemical method for measuring thiamin in the body has been perfected the question of the importance of thiamin deficiency in causing accentuation of heart failure of organic origin cannot be answered. Clinically we have encountered patients with hypertensive and chronic rheumatic heart disease in whom severe congestive failure has been precipitated on repeated occasions by lack of proper food or by the consumption of large amounts of alcohol.

Treatment. Without well controlled conditions it is difficult to ascertain the response of patients with beriberi to various therapeutic measures. In some cases bed rest results in immediate improvement but in other circulatory collapse may occur unexpectedly while the patient is resting. As a rule the symptoms and signs of congestive failure disappear earlier than enlargement of the heart and electrocardiographic changes. The time element in improvement varies. Ordinarily patients with congestive failure of but a few weeks' duration respond rapidly to treatment while in those with chronic deficiency the improvement is much slower. In some patients mercurial diuretics or digitalis is efficacious but the maximal and most regular benefit is assured after bed rest and parenteral administration of thiamin usually in the form of hydrochloride salt. *The size of the dose which has been termed as empirically ranges from 10 to 30 mg and is administered three times daily.* Both thiamin and vitamin concentrates are effective orally but in severe cases it is advisable to administer the drug subcutaneously or intravenously because some of these patients suffer gastrointestinal and liver disorders which may interfere with the utilization of the vitamin. In about one to four days following the start of the treatment diuresis and improvement of dyspnea indicate the therapeutic efficacy of the drug. Rarely the electrocardiographic changes in man as in experimental animals become accentuated for a short time following treatment and temporary bradycardia and elevation of the arterial pressure may develop during the course of the treatment. Subsequently the venous pressure falls the vital capacity of the lungs tends to return to normal and the blood flow slows down. Reduction of the size of the heart and disappearance of the alterations in the electrocardiograms do not occur for days or even weeks after the onset of clinical improvement. The fact that the

myocardium in beriberi can develop hypertrophy hydropic degeneration and deposition of interstitial collagen indicates that prolonged thiamin deficiency like other vitamin deficiencies can change from an easily reversible to an irreversible or slowly reversible state. This explains the variation in the response of different patients to thiamin therapy.

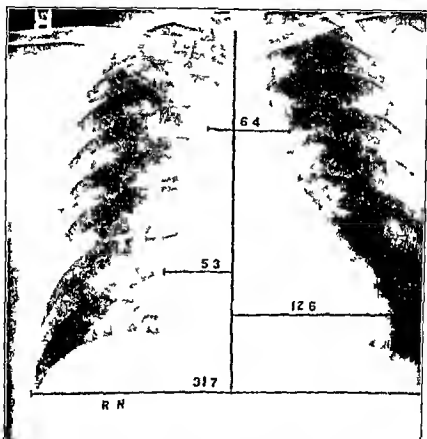


FIGURE 1. The cardiac silhouette in Case 1 (Weiss and Wilkins, *Ann Int Med*).

Thiamin therapy in our experience was without effect in cardiovascular disturbances of nonspecific deficiency origin. Similarly, edema responds to this medication only if it is of thiamin-deficient origin. Toxic side action from massive doses of thiamin are not known to occur. Because patients with beriberi usually have multiple deficiencies, attention should be paid to the simultaneous treatment of pellagra with nicotinic acid and other vitamin B complexes, anemia with iron or liver extract and hemorrhagic tendencies with ascorbic acid, vitamin K.

Illustrative Cases The following cases reported previously with Wilkins¹² illustrate the clinical characteristics of and the therapeutic response in beriberi

CASE 1 *Severe Congestive Failure of the Circulation, Mild Pellagra and Polyneuritis Fatal Circulatory Collapse* R. N. an odd job man aged 36 years had been drinking one half pint of alcohol daily for two years and one pint to one quart a day for three months. He had eaten a grossly

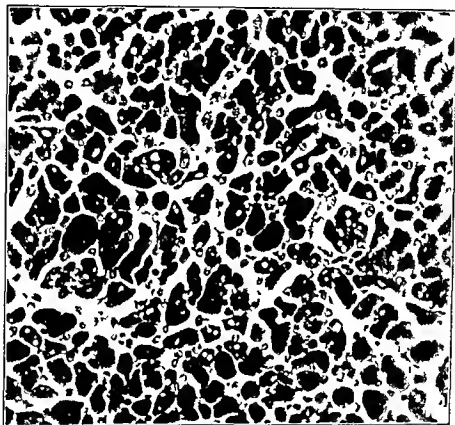


FIGURE 2 Hydropic degeneration of the muscle fibers in Case 1 (Weiss and Wilkins, *Ann Int Med*)

inadequate diet which became more deficient the more he drank. He complained of increasing dyspnea on exertion for one month, dependent edema for three weeks, hacking cough for ten days and orthopnea with insomnia for one day.

The family history and past history were noncontributory.

Physical examination revealed a well-nourished, slightly jaundiced man with severe orthopnea and diffuse edema, more pronounced in the dependent parts. There was pigmentation and scaliness of the skin on the dorsum of the hands and feet and on the lower legs. The veins of

the neck were engorged. The heart was percussed 12 cm to the left and 5 cm to the right of the midsternal line. A gallop was heard at the apex and a blowing systolic murmur at the base of the heart. The second sound at the pulmonic area was accentuated. The heart rate was 120 per minute and the rhythm was regular. arterial pressure 110 mm Hg systolic and 46 diastolic. Pistol sounds were audible over the carotid and



FIGURE 3. A Perivascular edema and separation of the muscle fibers in Case 1. B Separation of the muscle fibers by edematous collagen in Case 1. (Weiss and Wilkins Ann Int Med)

femoral arteries. The lower third of both lungs posteriorly was dull to percussion and over these areas and also anteriorly over the left hilar region moist rales were heard. The abdomen was protuberant and there was shifting dullness in the flanks. A firm liver edge was palpable 1 cm below the right costal margin. The spleen was not felt. Knee jerks were greatly diminished and ankle jerks were absent. Temperature 99° F. Respirations 36 per minute. Weight 183 pounds (usual weight 160 pounds).

Laboratory studies. Urine acid specific gravity 1.025, albumin trace, sugar 0, bile positive, sediment occasional leukocytes and hyaline casts. Blood hemoglobin 87 per cent, erythrocytes 4,430,000 per cu mm. Icterus index 11. Total protein content of the plasma 5.2 Gm per 100 cc, albumin 2.92 Gm and globulin 2.28 Gm, with calculated osmotic pressure 200 mm H₂O. The nonprotein nitrogen of the plasma was 6.6 mg

per 100 cc. The Hinton test was positive. The Takata Ara test was negative. Edema fluid from the thigh contained total protein 1.50 Gm. per 100 cc., albumin 1.10 Gm. and globulin 0.40 Gm.

A seven foot roentgenogram of the heart confirmed the clinical measurements (Fig. 1). The electrocardiogram was interpreted as within normal limits except for tachycardia. Special circulatory studies showed the venous pressure in the femoral and cubital veins to be 27 cm. H_2O , the circulation time 15.5 seconds, the femoral arteriovenous oxygen difference 0.75 volumes per cent, and the brachial arteriovenous oxygen difference 1.39 volumes per cent. The vital capacity was 2500 cc.

While this patient obviously was suffering from severe circulatory failure with rapid blood flow, he was made fairly comfortable with small doses of morphia. It was thought safe to withhold therapy until a control period had elapsed. There was subjective relief, but there were no changes in the edema or other signs of circulatory failure. On the third day the venous pressure had risen to 32 cm. H_2O . It was then decided to give vitamin B_1 , but before it could be administered the patient suddenly went into circulatory collapse from which he died.

Post mortem examination revealed marked anasarca and mild jaundice of all tissues. The heart weighed 590 Gm. The right auricle and ventricle showed marked dilatation and moderate hypertrophy, the left auricle and ventricle were normal. Except for the aortic cusps at the bases of which were minimal atheromatous thickenings, all valve cusps were thin, membranous and translucent. There was no evidence of rheumatic or luetic endocarditis. The coronary arteries, the epicardium and the pericardium were normal. The aorta showed minimal atheromatous change $\frac{1}{4}$ cm. above the aortic valve, but otherwise was perfectly normal.

The right lung weighed 1300 Gm. and the left 1080 Gm. The pleural surfaces were smooth and glistening but purple in hue. There were slight depressed scars at each apex. The crepitation was markedly decreased, giving the lungs a meaty consistency. The cut surfaces were uniformly purplish red throughout all lobes of both lungs. There was an extreme degree of edema and congestion and large quantities of serosanguineous fluid could be easily expressed. In the base of the right lower lobe was one small area of minimal bronchopneumonic consolidation.

The liver weighed 2180 Gm. It was firm, the surface smooth, its capsule thin and of normal translucence. Its cut surface showed a marked nutmeg appearance. The kidneys, spleen and other abdominal viscera were markedly congested.

The brain weighed 1560 Gm. There was atrophy of both frontal lobes, most pronounced in the pre- and post-central gyri. There were several very small petechial hemorrhages in Ammon's horn. The spinal

cord and peripheral nerves were normal in appearance. The rest of the gross examination was normal.

Microscopy revealed these additional findings. The right ventricle showed marked edema of the intermyocardial connective tissue with separation of the muscle fibers. There was also intracellular edema of the myocardium (Figs 2, 3A and 3B). The left ventricle showed marked increase in the collagenous connective tissue of the epicardium. There was an increase in the interstitial tissue especially that lying immediately beneath the epicardium. This connective tissue was extremely edematous causing separation of the myocardial cells.

The lungs showed marked dilatation and congestion of the capillaries of the alveolar walls. The alveoli contained many large macrophages filled with brown pigment, many extravasated erythrocytes and granular debris. In one area numerous polymorphonuclear leukocytes were present.

The liver showed extreme fatty degeneration. Many cells especially in the centers of the lobules were degenerated. There was no increase in connective tissue. No alcoholic hyaline was seen. The brain showed widespread perivascular hemorrhages and degenerative changes in numerous pyramidal cells.

CASE 2 Congestive Failure of the Circulation Polyneuritis Korsakoff's Psychosis Improvement on Vitamin B₁ W. E., an unemployed painter aged 50 years, was disoriented and confused and gave an unreliable history. He admitted taking one pint of pure alcohol daily for years and stated that he rarely ate anything. He was brought in by welfare workers from a cellar where he had been lying for weeks, unable to move. He had no complaints.

Physical examination revealed an extremely weak, poorly nourished man with diffuse edema which involved the sternum and face. He lay flat in bed in no apparent distress. The skin of the face showed marked acne rosacea with crusted pustular lesions. The skin of the extremities was dry, scaly and very warm. There was a pustular conjunctivitis and a small white ulcerous plaque on the right cornea. The pupils were quite small and reacted sluggishly to light. The tongue was smooth on the edges. There was moderate engorgement of the veins of the neck. The heart was percussed 11 cm. to the left and 6 cm. to the right of the mid sternal line. The sounds were of poor quality but there were no murmurs. The heart rate was 90 per minute and the rhythm was regular. The arterial pressure was 105 mm. Hg systolic and 75 diastolic. Sounds were audible over the carotid, femoral and brachial arteries. The lungs were resonant but moist rales were heard over the lower third of both lungs posteriorly. In the abdomen the liver edge was felt 1 cm. below the right costal margin. There was bilateral wrist and foot-drop. The biceps and triceps jerks were greatly diminished and the knee and ankle jerks were

not obtainable. There was marked muscle and nerve tenderness in the legs. Sensory examination was unsatisfactory but there was apparently hypesthesia of the lower legs. Temperature was 99° F. Respirations 23 per minute. Weight 158 pounds.

Laboratory studies. *Urine* acid specific gravity 1.012, albumin 2, plus sugar 0, bile 0, acetone 0, diacetic acid 0, pyruvic acid 0, sediment many leukocytes and hyaline casts. *Blood* hemoglobin 74 per cent erythrocytes

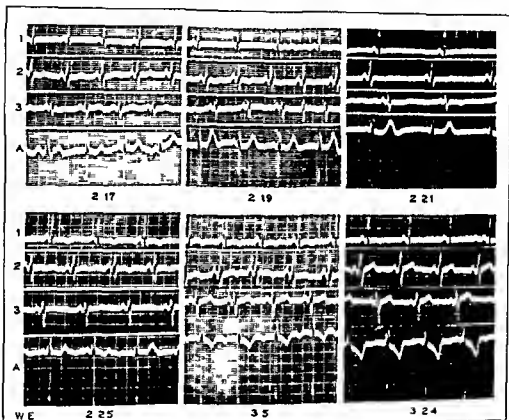


FIGURE 1. Electrocardiograms in Case 2. Note changes in amplitude of T waves (Weissenberg and Wilkins' Amplitude Method).

3,200,000 per cu. mm. leukocytes 9150, neutrophils 78 per cent. The fasting blood sugar was 144.5 mg. per 100 cc. and the nonprotein nitrogen 98 mg. The total protein content of the plasma was 5.3 Gm. per 100 cc., albumin 3.0 Gm., globulin 2.3 Gm., with calculated osmotic pressure 207 mm. H₂O. The icterus index was ten. The Hinton test was negative. The Takata-Ara test was positive. The bisulfite binding substances in the blood were 9.9 mg. per 100 cc. (as pyruvic acid). *Lidema fluid* from the arms showed a total protein content of 1.2 Gm. per 100 cc., albumin 0.66 Gm., globulin 0.55 Gm. *Lumbar puncture* revealed a spinal fluid pressure of 200 mm. H₂O, normal dynamics and a normal fluid.

Special circulatory studies showed vital capacity 1700 cc. venous pressure 17 cm H_2O circulation time 11 seconds and femoral arterio-venous oxygen difference 1.84 volumes per cent. The electrocardiogram (Fig 4) showed low voltage (7 mv) abnormal T waves and prolonged Q-T interval (k equals 0.47), interpreted as myocardial disease. The seven foot roentgenogram confirmed the enlargement of the heart found clinically (Fig 5).

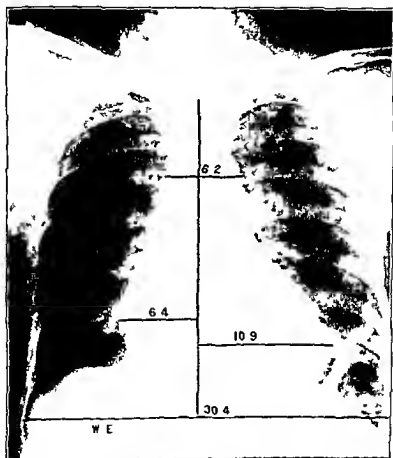


FIGURE 5 The cardiac shadow in Case 2 before treatment (Weiss and Wilkins Ann Int Med)

The patient was placed on a vitamin free diet fluids *ad lib* no other therapy. His course is graphically shown in Chart 1. On the second day it was found that he had retention of urine necessitating constant drainage. On the fourth day he lapsed into coma and appeared moribund. There had been no essential change in any respect of the circulation or blood chemistry. It was decided not to delay vitamin therapy. Accordingly 30 mg. of synthetic crystalline vitamin B_1 were administered intravenously. At that time the patient was in deep coma had Kussmaul

not obtainable. There was marked muscle and nerve tenderness in the legs. Sensory examination was unsatisfactory but there was apparently hypesthesia of the lower legs. Temperature was 99° F. Respirations 20 per minute. Weight 158 pounds.

Laboratory studies. *Urine* acid specific gravity 1.012, albumin 2 plus, sugar 0, bile 0, acetone 0, diacetic acid 0, pyruvic acid 0, sediment many leukocytes and hyaline casts. *Blood* hemoglobin 74 per cent, erythrocytes

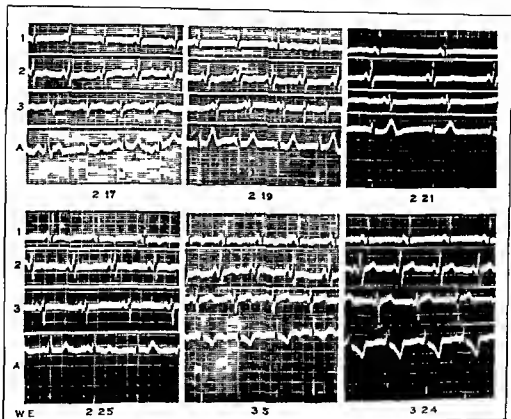


FIGURE 1. Electrocardiograms in Case 9. Note changes in amplitude and in T waves (Weiss and Walkus, *Ann. Int. Med.*)

3,200,000 per cu. mm. leukocytes 9150 neutrophils 78 per cent. The fasting blood sugar was 144.5 mg. per 100 cc. and the nonprotein nitrogen 98 mg. The total protein content of the plasma was 5.3 Gm. per 100 cc., albumin 3.0 Gm., globulin 2.3 Gm. with calculated osmotic pressure 207 mm. H₂O. The icterus index was ten. The Hinton test was negative. The Takata-Ara test was positive. The bisulfite binding substances in the blood were 9.9 mg. per 100 cc. (as pyruvic acid). *Lidema* fluid from the arms showed a total protein content of 1.2 Gm. per 100 cc., albumin 0.66 Gm., globulin 0.55 Gm. *Lumbar puncture* revealed a spinal fluid pressure of 200 mm. H₂O, normal dynamics and a normal fluid.

could not be established because while there were signs of dullness bronchovesicular breathing and moist rales over the hilar regions of both lungs posteriorly, these signs might have been due simply to increased pulmonary congestion resulting from compensation of the right ventricle out of proportion to the left. We have observed these signs without fever in similar cases and in this case the fever continued after the lungs had

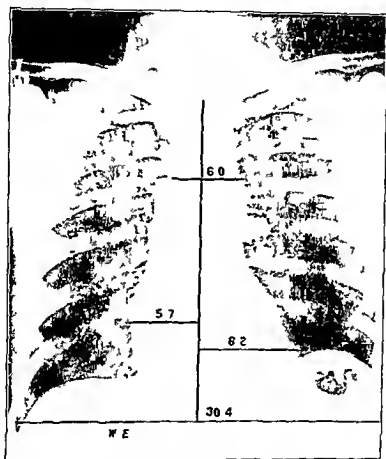


FIGURE 6 The cardiac shadow in Case 2 after treatment (Weiss and Wilkins Ann Int Med)

cleared and until the urinary infection was brought under control. The vital capacity decreased during this period but later returned toward normal. On the third day of vitamin therapy the nonprotein nitrogen, the bisulfite binding substances in the blood and the *QT* interval of the electrocardiogram were within normal limits. There was still no change in the venous pressure or the colloid osmotic pressure of the blood. Clinically, in spite of the fever, the extremities were now cool, the sounds had disappeared over the brachial arteries and were barely audible over

breathing and extremely small pupils which did not react to light. One hour and a half after the injection there was a most remarkable change. The patient aroused, asked for water, then took a large bowl of boiled milk and crackers. The breathing became normal, the pupils were dilated and reacted normally to light and on accommodation. Vitamin B₁ was continued both intravenously and subcutaneously, in large doses. In this case it seemed to have been lifesaving.

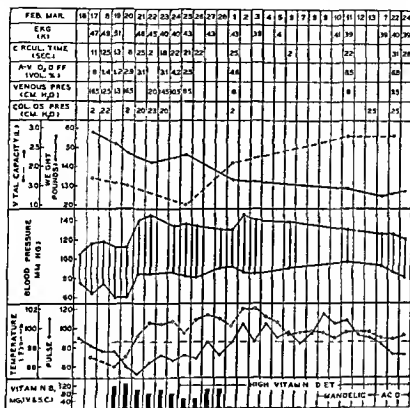


CHART 1 The clinical course in Case 2 (Weiss and Wilkins Ann. Int. Med.)

The next day the heart rate was 60 per minute, the circulation time 18 seconds, and the femoral arteriovenous oxygen difference 29 volumes per cent. The arterial pressure, venous pressure, and colloid osmotic pressure of the blood were unchanged. On the second day after vitamin B₁ therapy was instituted, the heart rate was as low as 52, the arterial pressure was 140 mm. Hg systolic and 84 diastolic, and the electrocardiogram (Fig. 4) showed increased voltage (10 mv). The circulation time was 25 seconds, and the arteriovenous oxygen difference 31 volumes per cent. The slowing of the circulation shown by these measurements was all the more remarkable in view of the fact that the patient now had a fever due to cystitis and also probably to bronchopneumonia. The latter diagnosis

could not be established because, while there were signs of dullness, bronchovesicular breathing and moist rales over the hilar regions of both lungs posteriorly, these signs might have been due simply to increased pulmonary congestion resulting from compensation of the right ventricle out of proportion to the left. We have observed these signs without fever in similar cases and in this case the fever continued after the lungs had

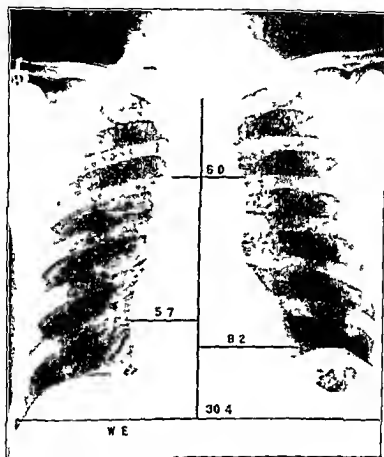


FIGURE 6 The cardiac shadow in Case 2 after treatment (Weiss and Wilkins Ann Int Med)

cleared and until the urinary infection was brought under control. The vital capacity decreased during this period but later returned toward normal. On the third day of vitamin therapy the nonprotein nitrogen, the bisulfite binding substances in the blood and the Q-T interval of the electrocardiogram were within normal limits. There was still no change in the venous pressure or the colloid osmotic pressure of the blood. Clinically, in spite of the fever the extremities were now cool, the sounds had disappeared over the brachial arteries and were barely audible over

the femoral arteries. There was less edema especially of the upper part of the body.

This patient's course was complicated by a prolonged febrile episode due to the stubborn cystitis which required forcing of fluids. Nevertheless he responded well to the vitamin therapy. On the sixth day of this treatment the edema had greatly decreased and the venous pressure was normal. The colloid osmotic pressure of the blood was still unchanged. He was then placed on a high vitamin diet and after four days the parenteral vitamin B_1 was discontinued.

Convalescence was steady and complete. The patient regained voluntary control of his bladder and the cystitis was relieved by mandelic acid. One month after admission a seven foot roentgenogram showed that the heart had decreased to normal size (Fig. 6). Except for a flat T wave in the first lead the electrocardiogram was normal (Fig. 4). The vital capacity was 2800 cc. The patient had lost a total of 34 pounds. In the fifth week the knee jerks returned and the strength was greatly improved. During the sixth week the patient was up and about the ward. He began to gain weight without edema. The protein content of the blood plasma was normal. Mentally although greatly improved he was still defective. His memory was poor and he confabulated. Consequently at the end of the sixth week he was committed to a sanatorium for chronic care.

CASE 3 *Congestive Failure of the Circulation and Polyneuritis Improvement After Vitamin B_1 Therapy*. J. S., a laborer aged 36 years had drunk one-half to one pint of whisky and many glasses of beer daily for 15 years. His food intake had been scanty and particularly deficient in vitamins. He complained of palpitation on exertion for three months of dependent edema for one month which had involved the scrotum for one day and of dyspnea on exertion for three weeks.

The family history was noncontributory. The past history was negative except for one previous hospital admission two years before for alcoholic gastritis.

Physical examination revealed a well nourished nervous man fairly comfortable in bed with marked edema of the scrotum and slight edema over the shins and sacrum. The color was quite florid and the skin was warm and moist. The heart was as percussed 12 cm. to the left and 5 cm. to the right of the midsternal line. The sounds were ticktack in quality and there was a short blowing systolic murmur at the apex. The heart rate was 110 per minute and the rhythm was regular. The arterial pressure was 110 mm. Hg systolic and 54 diastolic. Systolic sounds were audible over the carotid, femoral and brachial arteries. The lungs were resonant and clear except for moist rales at the left base posteriorly. The abdomen was negative. The knee jerks and ankle jerks were not obtainable. Temperature 99.2° F. Respirations 24 per minute. Weight 187 pounds.

Laboratory studies *Urine*, alkaline specific gravity 1.020 albumin sugar, bile and sediment negative *Blood*, hemoglobin 90 per cent erythrocytes 4,260,000 per cu mm, leukocytes 4700 neutrophils 61 per cent The nonprotein nitrogen was 32 mg per 100 cc The Kahn test was negative The Takata Ara test was negative The basal metabolic rate was plus four per cent

This patient was not seriously ill on admission indeed aside from the swelling of the scrotum there was no striking evidence of circulatory

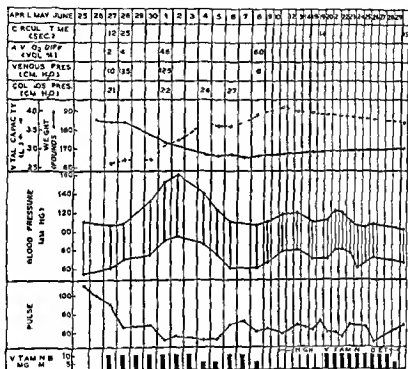


CHART 2 The clinical course in Case 3. Note the temporary elevation of the arterial pressure following the first but not the second course of crystalline vitamin B₁ (Weiss and Wilkins, Ann Int Med)

failure. He was placed on a low vitamin diet and all medication was withheld. On the third day there was no change clinically. Studies on that day showed the following: Weight 185 pounds, arterial pressure 106 mm Hg systolic and 60 diastolic, heart rate 90 per minute, vital capacity 2600 cc, venous pressure 10 cm H₂O, circulation time 12 seconds, the femoral arteriovenous oxygen difference 2.08 volumes per cent. The total protein content of the blood plasma was 5.07 Gm per 100 cc, the albumin 3.28 Gm and globulin 1.79 Gm, with a calculated osmotic pressure of 210 mm H₂O. The electrocardiogram showed no abnormality (Fig 7). A seven foot roentgenogram of the heart showed the heart enlarged as observed clinically.

After these observations vitamin B₁ was given intramuscularly in 5 mg doses twice daily. The clinical course and circulatory measurements are shown in Chart 2. The striking changes one day after the vitamin

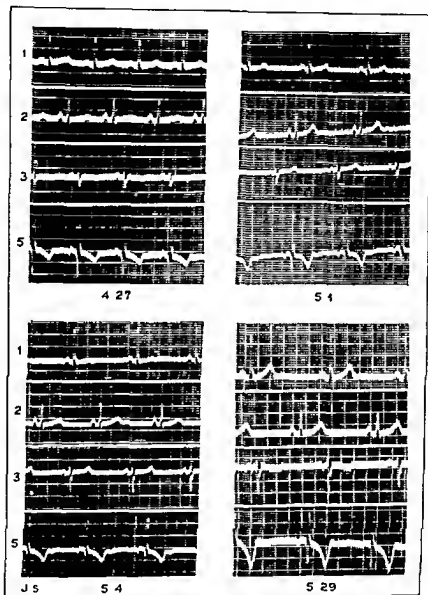


FIGURE 7. Electrocardiograms in Case 3. Note changes in T waves. (Weiss and Wilkins. *Ann Int Med*.)

were the slowing of the heart rate to 66 per minute and of the circulation time to 25 seconds and the increase in the femoral arteriovenous oxygen difference to 1.09 volumes per cent. The venous pressure had risen slightly to 13.5 cm H₂O. There was also a striking change in the clinical appear

ance of the patient. His face previously bright pink was now definitely cyanotic, the hands and feet were quite cool only the faintest sound could be heard over the carotid artery and no sound over the femoral or brachial arteries.

Four days after vitamin therapy was instituted the heart rate was 52 per minute the blood pressure had risen to 152 mm Hg systolic and 90 diastolic the vital capacity had increased to 3100 cc and the patient had lost 12 pounds of edema fluid in spite of the fact that there was no essential change in the venous pressure or colloid osmotic pressure of the blood. Marked clinical improvement coincided with these circulatory changes. In ten days following the vitamin therapy the patient had lost 20 pounds of weight and the vital capacity the blood pressure heart rate venous pressure and femoral arteriovenous oxygen difference had returned to normal. An interesting change in the electrocardiogram at this time was the inversion of the T wave in Lead I which subsequently reverted in normal (Fig 7).

At the beginning of the third week the parenteral injection of vitamin B₁ was stopped and a high vitamin diet started. The knee jerks returned in the middle of the fourth week. At the end of the fourth week a second course of parenteral vitamin B₁ was given exactly as before with no effect on any aspect of the circulation.

The patient was discharged well at the end of the sixth week.

CASE 4 Congestive Failure of the Circulation the Only Manifestation of Vitamin Deficiency When Treated With Digitalis and Diuretics Showed Little Improvement on Vitamin B₁ Striking Improvement J F an unemployed waiter aged 60 years for four years had spent but 30 cents a day on food which was grossly inadequate in vitamins. He had taken an average of ten glasses of ale and two glasses of whisky daily for one year. He complained of cough for six months dyspnea on exertion for one month orthopnea for two weeks increasing dependent edema for ten days and swelling of the abdomen for one week.

The family history showed that one brother died of alcoholism. The past history was noncontributory.

Physical examination showed an elderly apparently well nourished man with severe orthopnea and extreme dyspnea on the slightest exertion. His color was cyanotic but at times only slightly so. There was marked dependent edema up to the sternum. The skin of the face and extremities was warm and dry. There was moderate engorgement of the veins of the neck. The heart was percussed 11 cm to the left and 5 cm to the right of the midsternal line. There was a rough blowing systolic murmur heard over the entire precordium loudest at the apex. The heart rate was 120 per minute and the rhythm was regular except for occasional extrasystoles. The arterial pressure was 140 mm Hg systolic and 80 dias-

toxic. Loud sounds were heard over the carotid and femoral arteries. Percussion of the chest revealed diminished resonance posteriorly at both lung bases, where moist râles were heard. The abdomen was tensely distended, with shifting dullness in the flanks and a palpable fluid wave. No

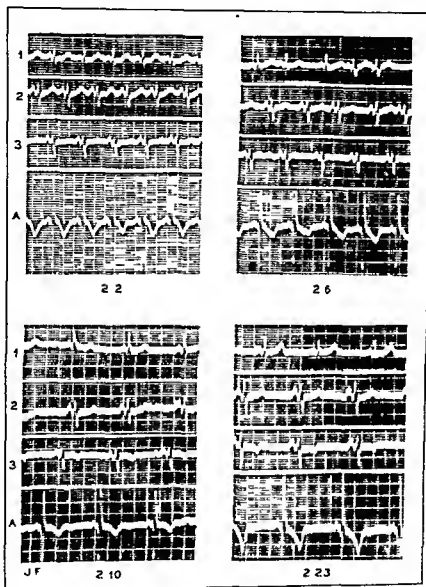


FIGURE 8. Electrocardiograms in Case 4. Note changes in rate and in T waves. (Weiss and Wilkins. *Ann Int Med*.)

organs were felt. The neurological examination was negative. Temperature 98° F. Respirations 30 per minute. Weight 181 pounds.

Laboratory studies. *Urine*, acid, specific gravity 1.015, albumin 0, sugar 0, bile 0, acetone 2 plus, diacetic acid 0, pyruvic acid 0, sediment

many leukocytes. Blood hemoglobin 85 per cent erythrocytes 3 700 000 per cu mm leukocytes 12 400 neutrophils 85 per cent. The nonprotein nitrogen was 28 mg per 100 cc the fasting blood sugar 94.1 mg per 100 cc and the carbon dioxide capacity 79.2 volumes per cent. The total protein content of the plasma was 4.8 Gm per 100 cc albumin 2.57 Gm globulin 2.23 Gm calculated osmotic pressure 178 mm H₂O. Icterus

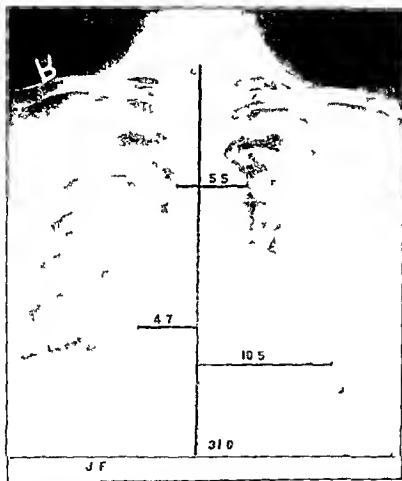


FIGURE 9 The card shadowgram in Case 4 before vitamin B₁ treatment (Weiss and Williams, *Ann Int Med*)

index 20. The Hinton test was negative. The Takata Ara test was positive. Bisulfite binding substances in the blood (calculated as pyruvic acid) were 12.89 mg per 100 cc. Edema fluid from the thighs showed a total protein content of 0.34 Gm per 100 cc albumin 0.09 Gm globulin 0.234 Gm. The vital capacity was 1000 cc and the venous pressure 17 cm H₂O. The electrocardiogram showed tachycardia low voltage (6 mv) and prolonged Q-T interval (k equals 0.52) suggesting myocardial disease (Fig. 8).

Because of the patient's precarious condition, his age, and the finding of a loud systolic murmur at the apex of the heart it was deemed wise to treat him at once with the standard cardiac drugs but to withhold vitamin therapy. Accordingly, he was put on a Karell diet (boiled milk), was digitalized rapidly and was given ammonium chloride, aminophyllin and salyrgan (two doses of 2 cc intravenously) as diuretics. Morphine was used as a sedative with marked subjective relief. There was a fall in pulse rate but no diuresis—the daily output ranged from 700 to 1100 cc.

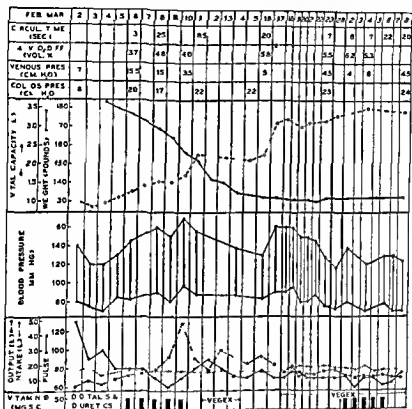


CHART 3 The clinical course in Case 1 (Weiss and Wilkins Ann Int Med)

This regime was maintained for four days and on the fifth day the following observations were made: Arterial pressure 145 mm Hg systolic and 82 diastolic, heart rate 80 per minute, venous pressure 15 cm H₂O, circulation time 13 seconds, femoral arteriovenous oxygen difference 3.66 volumes per cent. The vital capacity was 1250 cc. The total protein content of the blood plasma had risen to 5.38 Gm per 100 cc, albumin 2.67 Gm, globulin 2.71 Gm, producing a calculated osmotic pressure of 200 mm H₂O. This was evidence of hemoconcentration as the values two days later had fallen to and below their previous levels. A seven foot roentgenogram showed the heart still enlarged to the left and right (Fig 9).

On the fifth day *all medication* was omitted and the deficient diet continued unchanged. Synthetic crystalline vitamin B₁ was given in 10 mg doses subcutaneously five times a day. The next day the urine output was 1500 cc and rose progressively to reach a peak of 4800 cc four days after the vitamin was started.

The clinical course and circulatory measurements are shown in Chart 3. Of particular interest on the second day after vitamin therapy were the elevation of the blood pressure to 160 mm Hg systolic and 90 diastolic, the slowing of the heart rate to 60 per minute, the increase in the circulation time to 25 seconds and the increase in the arteriovenous oxygen difference to 4.8 volumes per cent. The venous pressure and colloid osmotic pressure of the blood were still essentially unchanged but subsequently became normal as did the blood pressure, the heart rate and other aspects of the circulation.

The clinical improvement coincident with these changes was dramatic. Except for a brief febrile episode with signs of bronchopneumonia on the sixth day after vitamin treatment, the course was one of steady improvement. The patient lost 51 pounds of weight in 12 days. He was then seen to be a thin faced, frail individual rather than the well nourished man he had seemed on admission. The cyanosis, the orthopnea and the dyspnea on exertion disappeared while the vital capacity rose to a normal value.

On the eleventh day a high vitamin diet was begun. In the fifth week when all the circulatory measurements had been normal for one week the same course of vitamin B₁ was repeated with no effect whatever. The patient was discharged well at the end of the fifth week. The seven foot roentgenogram (Fig. 10) showed that the heart had returned to normal size.

CASE 5: Congestive Failure of the Circulation, Cardiac Asthma, Polyneuritis, Mild Psychosis, Improvement on High Vitamin Diet and Continuous High Alcohol Intake. O. O., a corsetiere aged 37 years, had consumed one pint of whisky daily for seven years. Her diet was meager, rarely contained vegetables or meat and consisted principally of coffee, tea and sandwiches of white bread.

She complained of intermittent weakness and numbness in the feet for six years, increasing and progressing upward to involve the legs and finally the hands for three months. For two years she had had palpitation and dyspnea on exertion and for one year swelling of the ankles. She also complained of orthopnea for three weeks and nocturnal attacks of paroxysmal dyspnea for two weeks.

The family history revealed that the paternal relatives were alcoholics; otherwise it was noncontributory. The past history was noncontributory.

Physical examination showed a well nourished mildly psychotic, apprehensive, orthopneic woman with marked edema of the legs. The skin was thick, warm and moist. The veins of the neck were distended. The heart was percussed 11 cm to the left and 5 cm to the right of the midsternal line. There was a gallop and a short blowing systolic murmur.

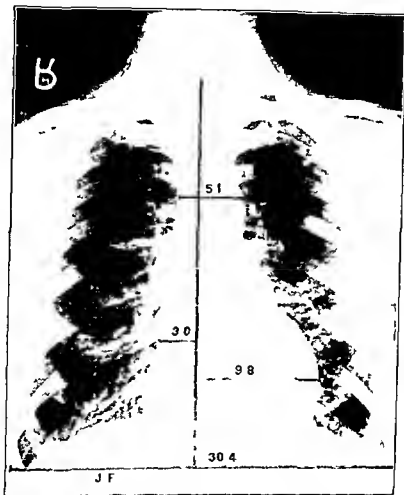


FIGURE 10 The cardiac shadow in Case 4 after improvement. (Weiss and Wilkins, *Ann Int Med*)

at the apex. The heart rate was 120 per minute and the rhythm was regular. The arterial pressure was 110 mm Hg systolic and 70 diastolic. The carotid and peripheral arteries showed increased pulsations. The lungs were resonant and clear. In the abdomen the liver edge was felt just below the right costal margin. There was bilateral toe drop, absent knee and ankle jerks, and absent vibration sense below the knees. Temperature 99° F. Respirations 25 per minute. Weight 167 pounds.

Laboratory studies *Urine*, acid specific gravity 1.019 albumin 0 sugar 0 sediment many leukocytes *Blood* hemoglobin 82 per cent erythrocytes 4,230,000 per cu mm leukocytes 9300 neutrophils 76 per cent The nonprotein nitrogen was 60 mg per 100 cc of blood The total protein content of the plasma was 6.5 Gm per 100 cc albumin 3.25 Gm, globulin 3.25 Gm with calculated osmotic pressure 264 mm H₂O The Kahn test was negative Roentgenogram confirmed the enlargement of the heart and showed congestion of the lung fields Electrocardiogram (Fig 11) showed tachycardia and abnormal T waves suggesting myocardial disease

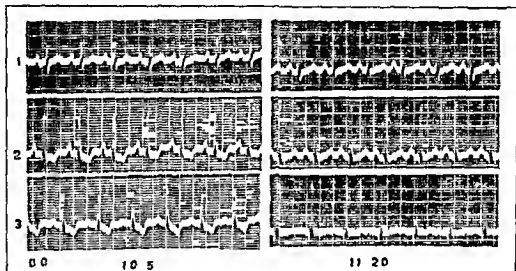


FIGURE 11. Electrocardiogram in Case 5. Note the return of the ST complexes to normal following the continued administration of oral vitamin B concentrate and alcohol (Weiss and Wilkins. *Ann Int Med*).

For five days the patient was kept on a house diet with no essential change in her condition. She was then placed on a high vitamin diet supplemented by oral yeast extracts and intramuscular liver extract. In addition she was given one pint of whisky a day. On this régime she improved rapidly. The nocturnal dyspnea, the edema and palpitation disappeared. Within two weeks the heart rate had decreased to 90 and the gallop had disappeared. After six weeks the electrocardiogram was normal (Fig 11). There was slower but steady improvement in the neurological and mental symptoms. When discharged from the hospital four months after entrance she was able to walk satisfactorily and the psychosis had cleared but some abnormal neurological signs still persisted in the legs. She had continued to receive one pint of whisky daily until discharge.

CASE 6. Acute Cardiac Dilatation and Congestive Failure Associated with Polyneuritis. Improvement After Rest, Digitalis, Good Diet and

Oral Vitamin B Extract W F a laborer aged 32 years had consumed half a pint of pure alcohol daily for five years. He had eaten little food because of an extremely poor appetite. He complained of increasing dyspnea on exertion for two years, increasing swelling of the legs for one year and difficulty in walking associated with numbness of the feet and hands for six months. The family history and the past history were non-contributory.

Physical examination revealed a small but well-nourished man comfortable flat in bed with marked edema of the lower legs. The skin was dry, warm and of good color. The veins of the neck were distended and showed marked pulsations. The heart was percussed 11 cm to the left and 6 cm to the right of the midsternal line. The precordium was heaving rapidly. A marked gallop was heard near the apex where there were also loud rough systolic and diastolic murmurs. Over the aortic area blowing systolic and diastolic murmurs were heard. The heart rate was 100 per minute and the rhythm was regular. The arterial pressure was 130 mm Hg systolic and 60 diastolic. There were marked pulsations of all peripheral arteries over which loud pistol sounds were audible. The lung bases were dull posteriorly. In the abdomen the liver was palpated 1 cm below the right costal margin. The knee and ankle jerks were not obtainable. Temperature 100° F. Respirations 20 per minute. Weight 113 pounds.

Laboratory studies. *Urine*, first specimen acid, specific gravity 1.036, albumin 0, sugar 3 plus bile positive, acetone 0, diacetic acid 0, sediment negative. Later specimens negative. *Blood*, hemoglobin 78 per cent, erythrocytes 1,220,000 per cu mm, leukocytes 9800, neutrophils 65 per cent. The nonprotein nitrogen was 22 mg per 100 cc, the fasting blood sugar on the third day 93 mg per 100 cc. The total protein content of the blood plasma was 6.3 Gm per 100 cc, albumin 3.1 Gm, globulin 2.9 Gm, with calculated osmotic pressure 260 mm H₂O. The Kahn test was negative. The Trikata Ala test was negative.

A seven foot roentgenogram of the heart on the second day showed enlargement (Fig. 12). The electrocardiogram showed a flat T wave in Lead I and prolonged Q-T interval (k equals 0.46) interpreted as myocardial disease.

Because of the diastolic murmurs heard on admission it was thought that the patient had organic valvular heart disease. He was digitalized rapidly and given a high vitamin diet supplemented by oral extracts of vitamin B. On the second day no diastolic murmur could be heard. The improvement was rapid. On the seventh day he was allowed out of bed. The digitalis was omitted. A seven foot roentgenogram at the beginning of the fifth week (Fig. 13) showed a small heart. He was discharged well in the sixth week.

CASE 7 *Repeated Admissions for Attacks of Cerebral Sinus Syncope and Circulatory Failure Associated With Polyneuritis Relief After Diet and Extracts Rich in Vitamin B* E S an unemployed odd job man aged 47 years had drunk one pint to one quart of liquor daily for years. He had eaten irregularly and his diet was of poor quality. He was admitted to the hospital on three occasions with essentially the same

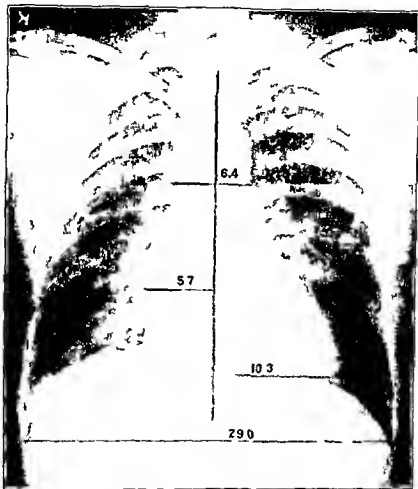


FIGURE 10 The cardiac shadow in Case 6 on the first day after admission
(Weiss and Williams, *Ann Int Med*)

complaints. These were dizziness and attacks of syncope, soreness of the mouth and tongue, pain, weakness and numbness in the legs, nocturnal cough, dyspnea on exertion and nocturnal attacks of paroxysmal dyspnea.

Physical examination revealed a poorly nourished man with no orthopnea or edema. The skin was pale. The mucosa of the mouth and tongue was red with patchy ulcerated areas covered by whitish exudate. The heart was percussed 7 cm. to the left and 3 cm. to the right of the

midsternal line. There was a blowing systolic murmur at the apex. The heart rate was 110 to 120 per minute, and the rhythm was regular. The arterial pressure was 115/70 to 120/90 mm Hg. The abdomen was negative. The ankle jerks were not obtainable and the vibration sense was absent below the knees. Temperature 99° to 100° F. Respirations 20 to 25 per minute. Weight 135 to 115 pounds.



FIGURE 15 The cardiac shadow in Case C following improvement. (Weiss and Wilkins. *Ann Int Med*.)

Laboratory studies. *Urine*, acid specific gravity 1.020, albumin, bile sugar and sediment negative. *Blood*, hemoglobin 55 per cent, erythrocytes 4,000,000 per cu mm, leukocytes 5700, neutrophils 71 per cent. The nonprotein nitrogen was 30 mg per 100 cc. The Kahn test was negative. *Lumbar puncture* revealed normal pressure and normal spinal fluid. *Gastric analysis* showed no free acid after histamine. The seven foot roent-

genogram showed no abnormality of heart or lungs. The electrocardiogram showed flattening or inversion of the T waves in Leads I and II interpreted as myocardial disease.

On each admission under treatment with a good rest, intramuscular liver and vitamin B extracts there was complete relief of the cardiovascular symptoms within two weeks. It is of interest that with improvement the blood pressure rose from 140/104 to 200/120 mm Hg. The improvement in the neurological symptoms was equally striking but slower.

On the second admission it was found that even mild stimulation of the carotid sinus caused complete asystole of the heart and syncope. The patient stated that the induced attack was the same as the spontaneous spells of which he complained. Six days after vitamin therapy the dizziness had improved and carotid sinus pressure now induced no asystole but an idioventricular rhythm with a rate of 30 per minute. Slight dizziness but no syncope accompanied the slowing. Four days later and there after stimulation of the carotid sinus induced only transient physiological slowing of the sinus rhythm and no dizziness. He was discharged improved in the third week.

SCURVY

The generalized hemorrhagic tendency in scurvy can cause hemorrhagic pericardial effusions—a complication rarely seen in scurvy in this country. Hift and Brull³ observed acute recurrent hemorrhagic pericarditis among the scorbutic inmates of a Russian concentration camp in Siberia. Of 325 cases of scurvy, 28 showed severe pericardial effusion with secondary congestive failure of the circulation. In six the pericardial effusion was fatal.

Changes in the myocardium in human scurvy have been described but it is questionable whether such changes can be attributed to ascorbic acid deficiency. Thus when Erdheim⁴ performed post mortem examination on 31 Viennese children who died as a result of scurvy in the famine year of 1918, he noted that cardiac hypertrophy and dilation were present in these children and called the heart Barlow Herz. The myocardial hypertrophy was moderate in eight, considerable in seven and enormous in six. It is regrettable that Erdheim failed to include clinical data and histologic examinations. He does mention, however, that duration of malnutrition in these cases was long and that many of the children were marantic and suffered from diarrhea. In view of the fact that osteoporosis was also present and from what we know today of the fre-

quent occurrence of multiple deficiency it seems probable that the cardiac disease in these cases was caused by beriberi. It seems probable too therefore that the cardiac changes and disturbances described by some observers in scurvy as well as in rickets and pellagra are attributable to a coexisting thiamin deficiency.

The literature of recent years bearing on the relation of *ascorbic acid deficiency to rheumatic fever and rheumatic heart disease* is interpreted as follows. In rheumatic fever as in other chronic infections the supply of ascorbic acid in the blood is low due either to inadequate intake or to increased utilization with the result that the body is partially depleted of its normal storage. The capillary fragility of some patients with this deficiency is increased but can be remedied by the administration of ascorbic acid. On the other hand in our opinion and experience ascorbic acid fails to influence the clinical course or reduce the incidence of recurrent attacks of rheumatic manifestations and a causative relationship between ascorbic acid and rheumatic fever does not therefore exist. In spite of this negative correlation it seems advisable in order to assure optimal nutrition to feed rheumatic patients with a balanced diet rich in vitamins including ascorbic acid.

The increased vascular fragility in ascorbic acid deficiency can lead to extensive hemorrhages in various tissues. The fact that the ascorbic acid level in the blood of persons with chronic alcoholism is frequently low explains the tendency in these patients to vascular fragility and the occurrence of epidural, subdural and intracerebral (polyencephalitis hemorrhagica Vernicke) hemorrhages without trauma or in relatively slight traumatic conditions. The same mechanism may play a role in the hemorrhagic birth injuries.

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infectious condition which may be accompanied by such disease e g rheumatic fever tonsillitis chorea syphilis etc

Classes I II A and II B form the major groups then with which we shall deal This is to say that we have to do almost altogether with the chronic stages of inflammatory and degenerative heart disease with or without congestive heart failure but if with failure then of a degree that permits at least of mild activity The type and degree of therapy must be and



FIGURE 9 Saratoga Springs The Island Spout and the cascades of mineral deposits

visualized and conform to the considered judgment that follows careful examination and estimate of myocardial competence Patients in Class III who are unable to carry on any physical activity though some mild forms of massage and certainly to rest do not comprise any but a small portion of the field of endeavor to be considered Their problem will be dealt with presently The cardiac neuroses are particularly suited to physical therapy

CHAPTER XLII

PHYSICAL THERAPY IN CARDIOVASCULAR DISEASE

By CARL R. COMSTOCK M.D. and WILLIAM D. STROUB M.D.

Introduction The pressing problems of acute disease have been clarified to a material degree and a greater consciousness of the need of the chronically ill has arisen in the thinking medical mind. The avenues of approach to this problem in the field of therapy are not many and of these that of physical therapy has taken on an increasing importance because of simplicity, directness of purpose and oftentimes of effectiveness.

The testing ground for various procedures has been in the larger hospitals and more specially at the various spas of Europe and the United States. We are indebted particularly to what comprises the present Germany and to France for the major development and elaboration of suitable forms and the earlier recognition of their value.

Because of foreign travel and study on the part of the American physician and because of his increasing awareness of the problem of chronic disease a growing interest in the development of physical therapy and its suitable application has been aroused. This is evidenced by a notably enlarged patronage at the few spas in the United States where suitable accommodation and facilities are available for groups of varying economic levels. At Saratoga Springs for instance where the State of New York has created an extensive development the records for the years 1932 to 1937 show an interesting increase in the number of treatments at the spa. For the year 1932-1933 there were 97,018 which number has so grown that in the year 1936-1937 116,511 were given. It is noteworthy that a large percentage of the patients taking these treatments were referred by physicians.

The field of application of physical therapy in cardiovascular disease limits itself rather sharply to certain of the New York Heart Association's

(1291)

classifications Since these classifications will be referred to frequently during this chapter, the writer is giving them now

CLASS I Patients with organic heart disease who are able to carry on their habitual physical activity

CLASS II Patients with organic heart disease who are able to carry on diminished physical activity

A Slightly decreased

B Greatly decreased

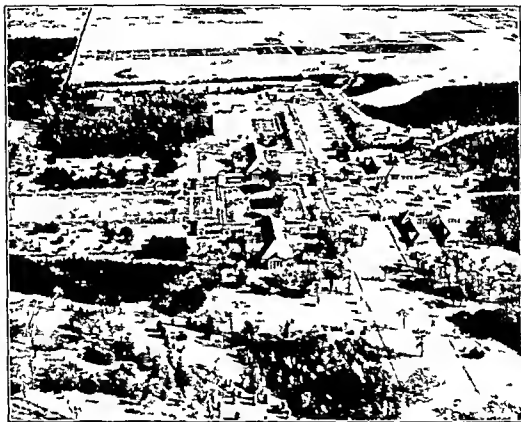


FIGURE 1 Aerial view of the new Saratoga Spa

CLASS III Patients with organic heart disease who are unable to carry on any physical activity

CLASS E Patients with possible heart disease Patients who have abnormal physical signs in the heart, but in whom the general picture or the character of the physical signs leads us to believe that they do not originate from cardiac disease

CLASS F Patients with potential heart disease Patients who do not have suggestion of cardiac disease, but who are suffering from an

infectious condition which may be accompanied by such disease *e g* rheumatic fever tonsillitis chorea syphilis etc

Classes I II A and II B form the major groups then with which we shall deal This is to say that we have to do almost altogether with the chronic stages of inflammatory and degenerative heart disease with or without congestive heart failure but if with failure then of a degree that permits at least of mild activity The type and degree of therapy must be indi-

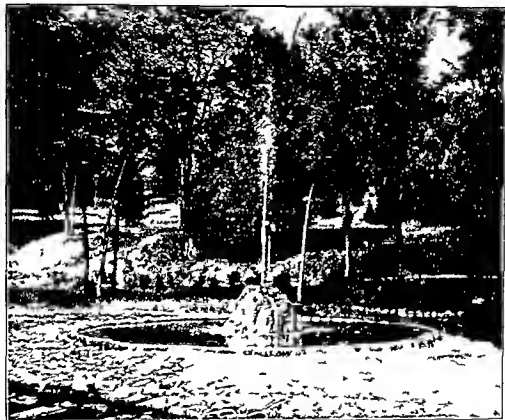


FIGURE 2 Saratoga Springs The Island Spouter with its interesting mineral deposits

vidualized and conform to the considered judgment that follows careful examination and estimate of myocardial competence Patients in Class III who are unable to carry on any physical activity though suited to mild forms of massage and certainly to rest do not comprise any but a small portion of the field of endeavor to be considered Their problem will be dealt with presently The cardiac neuroses are particularly suited to physical therapy

THE VARIOUS FORMS OF PHYSICAL THERAPY

REST

One brings up the subject of rest first because it plays so large a part in the restoration of cardiac competence and in the arrest of the progress of cardiovascular disease. It is indeed the simplest of all forms of physical therapy but incorporates more than appears at first consideration. It implies not only physical rest but too that state of mental equilibrium which is best expressed by the term calm philosophy of life. It implies a controlled emotional state that permits true relaxation. It implies freedom from problems to be solved and from moral obligations to be met. It implies too suitable recreation. To bring all of these about requires understanding of the individual problem on the part of the physician and no little time in intimate and friendly consultation.

The amount of physical rest needed can be determined best by the status of the myocardium and its response to effort. When complete bed rest is not indicated it falls naturally into periods following major meals and varies in amount. One or two hours after luncheon are particularly indicated and often a half hour before dinner is advisable. A quiet period after the evening meal is essential though it need not necessarily imply bed rest. In the writer's experience games that tend to excite or to create problems are inadvisable during this period since often they are conducive to poor sleep. Reading which can be given up easily is permissible and the enjoyment of music most satisfactory. Eight or nine hours of sleep at night are requisite and breakfast in bed is not only pleasant but frequently indicated. Often one day a week spent in bed is an excellent investment of time.

Mental and emotional rest many times is difficult to achieve at home and under such circumstances a sojourn of three or four weeks in a new and desirable environment can be productive of very real benefit. This is especially true of a visit to one of the various spas where not only competent medical supervision is available but there is also provided ample means for physical therapy and suitable recreation.

EXERCISE

White¹ states that it is important generally to allow a patient with heart disease to take as much exercise as he reasonably and safely can with periods of rest perhaps of a few days each because it is physical exercise that helps to maintain a state of general good health and un-

doubtedly the proper functioning of the peripheral circulation resulting from reasonable exercise aids the heart in its work. The most practicable exercise is walking and this is also quite uniformly good—it can be graded easily by three factors—distance, speed and grade (hill climbing). Other mild exercises like easy golf and croquet may be encouraged at times. It is acceptable then that the cardiovascular system is benefited by that amount of exercise which it can undertake without embarrassment for it is altogether conceivable that the myocardium will find itself in the same status as the general musculature. Mackenzie² states that the guide in these persons is the patient's response to effort. It may be taken for granted that effort which he performs with comfort is not harmful but beneficial in the sense that exercise of the heart muscle within the limits of its power keeps the muscle in good condition.

Although difficult to demonstrate by controlled experiment it is generally accepted that active or voluntary exercise is of more benefit than is any passive or involuntary form although in cardiovascular disease falling in Class III this latter often is all that can be undertaken and is then a valuable procedure.

In considering the matter of suitable active exercise in cardiovascular disease it must be emphasized again that the type and duration is to be dictated by a careful estimate of myocardial capacity and runs the gamut from brief slow walks on level ground to anything as strenuous as singles in tennis. The need for exercise however is only in the amount which will keep the individual in good muscular tone and for this that amount represented by walking at moderate pace for one to two hours daily is ample. Anything beyond this is for the pleasure of the patient only and should be controlled by circumstance. Evidences of shortness of breath, precordial discomfort or sense of exhaustion dictate distance and rate of walking or degree of other forms of exercise and a clear understanding of the significance of these symptoms on the part of the patient is imperative.

To some golf sugarcoats the pill of exercise and the game lends itself readily to work of varying amount in a most satisfactory manner. The course should be reasonably flat—that is with no gradient over five degrees and the holes not too long. The variants given range from putting through pitch and putt the irons woods to a full nine holes and are particularly enjoyed by the executive and professional types. No com-

petitive spirit should be allowed to enter the picture, however. Croquet and archery are other suitable forms of diversional exercise.

At most of the European spas and at some of those in America carefully graded walks of the Stokes-Oertel hill-climbing type have been laid out. The course consists usually of some twenty walks beginning with $\frac{1}{12}$ mile on a three per cent grade and progressing gradually to two miles at a 5 per cent grade. This type is useful particularly in the obese with good myocardial reserve and is carried out in conjunction with reduction measures, i. e., restrictions in diet and limitation of fluid intake. It is of value in the suitable case but calls for intimate supervision of the individual. The usual duration of this type of treatment in this country is three to four weeks, but when circumstance permits is prolonged to six or eight and is often complemented by massage and Turkish baths. It has been the writer's experience that walking graded as to duration and rate but on average level terrain serves as useful a purpose and is more adapted to the American temperament. In conjunction with dietary restriction and accessory treatments such as massage and the Turkish bath the results have been equally good and the number of untoward events less likely.

The Schott Exercises: During the latter part of the last century Doctors August and Theodor Schott³ of Bad Nauheim developed a series of resistance exercises for the increase of myocardial reserve in those patients with moderate to material degrees of lessened capacity. These exercises were designed to produce regulated movements with but little exertion and no fatigue. They are exercises with resistance and require the services of a trained operator. They have been used but little in this country because of their complicated nature and because of the lack of attendants familiar with them. They are soundly conceived and are of material use in well-chosen cases. There follows a summary of the more important regulations which govern them:

1. Passive resistance movements include abduction, adduction, flexion, extension and rotation in a vertical, horizontal or lateral direction.
2. These movements should so alternate that new groups of muscles are continuously made to act in sequence, thus avoiding fatigue.
3. The resistance should be made by the operator as slowly and gently as possible, but with as much firmness and muscular power as the patient's physical condition will warrant.

4 The operator should never grasp the patient's limb tightly but should oppose its movement by firm counterpressure against the advancing side thus retarding the movement but always permitting the patient to retain the balance of power

5 The operator should change his resistance whenever the direction of the physical force is changed

6 To gain a well balanced and uniform effect these exercises should always be bilateral

7 The operator should closely watch the patient's breathing and circulation and at the slightest sign of embarrassment should stop the exercises The patient should never be allowed to hold his breath while exercising

8 A pause of one or two minutes should be allowed between each exercise in order to avoid any fatigue The patient may sit down during the pause especially during the latter half of the seance

9 The length of time devoted to each seance should be about a half hour

10 After the seance is finished the patient should rest quietly on a couch for at least 15 minutes

Each movement is to be performed slowly and evenly and no movement is repeated twice in the same limb or group of muscles Each single or combined movement is followed by an interval of rest The movements are not permitted to accelerate the patient's breathing and the operator watches the face for indications of cardiac embarrassment notably dilatation of the alveolar cyanosis or pallor of cheeks and lips yawning sweating and palpitation The appearance of any of the above evidences of distress are the signal for the cessation of the movements

Since it is realized that these movements are to be utilized in patients with materially damaged hearts the importance of strict adherence to these precautions is evident

PASSIVE EXERCISE

In their simplest and most practical forms passive exercises consist of flexion extension rotation abduction and adduction of the four extremities These are performed by a trained operator who supports the limb being exercised and causes it to be moved in the several directions beginning usually with the feet then the lower leg and finally the whole leg etc etc It is done without any effort on the part of the patient The exercise is repeated one or more times according to the physician's opinion of the individual capacity It is given in the dorsal position and is utilized especially as an initial procedure in Class III patients

Mechanotherapy Mechanotherapy finds its greatest indication in Class II B, but cannot be utilized to best advantage except where large installations of the so-called Zander apparatus are available. This limits naturally the opportunity to certain of the larger hospitals and to the spas where such installations exist. There are some real objections to the use of the machine for passive exercise as against the use of the Schott resistance exercises, their purpose being essentially the same. The machine does not feel or think. It is arbitrary in its action. Furthermore the equipment is expensive and many types are needed to accomplish the various movements of groups of muscles, a thing better and more intelligently done by a trained attendant. Although the writer has had access to a fairly large installation he has had occasion to use it but seldom. The universal tendency of the past few years has been toward simplification and the development of manual operation.

Massage Massage has become one of the most frequently used forms of passive exercise and has found a really important place in the treatment of cardiovascular disease. In one or another of its various types it can be of real help in the treatment of heart disease.

Massage consists of one or more of the following procedures which are usually prescribed to be given in a light, medium or heavy manner:

1 Effleurage—a light stroking motion given in the direction of venous flow. It is of particular use as a beginning procedure for the bedridden cardiac and should be given in the dorsal recumbent position.

2 Stroking—a procedure of the same type but using a direction from the center to the periphery. It is for purposes of relaxation.

3 Kneading—in which by circular movements of the hand the skin and superficial tissues are made to move on the deep tissues. It may be used with or without friction.

4 Vibrations are fine tremor movements of the hand, the arm being relaxed. It is a useful procedure in the more serious situations and may be utilized too in the form of electrical vibrations.

5 Stimulating massage is best described as shaking, hacking or clapping movements. Shakings are similar to vibrations but are coarser and heavier. Hackings are produced by sharp blows of the ulna border of the hand and the last two fingers repeated rapidly for a limited number of times. Clappings are blows given with the palm of the cupped hand.

6 Massage sous l'eau or the Vichy douche, which is a massage incorporating effleurage, kneading, hacking and cupping and given under a spray of warm water, is a variant which is thought to cause a greater redistribution

of blood because of its association with heat. In the writer's experience and for practical purposes it does not replace or improve upon regular massage. It is a pleasant procedure to be undertaken at a spa.

In most instances a prescription for massage will call for a combination of the various movements above mentioned. It is well to specify the number, degree and duration, but a well-trained masseur familiar with the handling of cardiac patients will make but few mistakes. Massage, however, is capable of causing great fatigue and the degree produced, if any, will guide the physician in further prescriptions. The use of the various forms must be governed by good sense and observation, and should always be followed by a rest period.

Nylin,⁴ in a paper on physical exercise in cardiac conditions, has summarized the matter in a most satisfactory manner. He says, "Active exercises stimulate the heart to increased work. If performed gently, slowly, evenly and with sufficient rest between movements, they aid more than stimulate the heart in its work, provided cardiac insufficiency is not too pronounced. They act on the blood vessels as do passive exercises and stimulate respiratory movements to increased activity, facilitating pulmonary circulation. On the other hand, active exercises enhance the work of the heart, and the more vigorous the exercise, the greater the effect. These two different effects allow grading of the exercises to meet the demands of each individual cardiac condition, provided the heart has enough reserve power to tolerate some increase in its work. Neglect of this individualization leads to disappointing results. Especially in the beginning of treatment, the physician should study the effect of the exercises and modify them according to the needs of each successive stage of the disease. More than the usual amount of rest and, in some cases, total curtailment of the patient's activities are essential in any program of exercise for cardiac patients; this program must include mental rest and freedom from anxiety.

"When the heart is unable to maintain a fairly normal circulation even during rest or causes severe dyspnea during rest, the patient is confined to bed and gentle massage (stroking) and passive movements are indicated. Most patients respond favorably to systemic massage. When general massage is not well borne, only the extremities are manipulated until improvement allows general massage. The patient is never prone during massage. During this stage of the disease, passive movements given

with a slow even rhythm are limited to the toes ankles fingers wrists and elbows under complete relaxation therefore the extremity must be well supported by the operator The procedure for each treatment consists of two or three deep respirations massage to one leg passive movements of toes and ankle of this leg two or three deep respirations pause of one or two minutes This is then repeated with the other leg and then with each arm Effleurage of the trunk follows and treatment is concluded with three or four deep respirations With improvement kneading movements to the extremities are added and the passive exercises are extended to the hip and shoulder joints at first with a limited range of movement which is gradually enlarged in accordance with the improvement of the patient

When reserve power of the heart is sufficiently increased active exercises are instituted These are in the nature of either free or resistive movements The response of the cardiovascular system must be watched carefully If the increase in the pulse rate and in the blood pressure persists more than two or three minutes after the exercises or if there is resulting shortness of breath palpitation arrhythmia or precordial pain the exercises must be discontinued or less vigorous movements must be substituted until the heart is stronger *Best results are obtained when there is a correct proportion between the demand of the exercises on the heart and the degree of cardiac reserve power*

No standard program for exercises can be given but the following rules must be strictly observed (1) There should be an interval of at least one hour between a meal and the exercises (2) No exercises should be taken in the evening (3) Treatment must be progressive (4) In the beginning exercises are taken in the supine position later in the sitting and then the standing position (5) The force of gravity must be considered in execution of the exercises The operator may have to assist movement in upward raising of the leg or trunk and may have to resist it in lowering the part to the horizontal position (6) Uni or bilaterality of exercises of the extremities and their range must depend on the amount of cardiac reserve power (7) An individual exercise is not repeated in the same part of the body but the whole set of movements may be repeated if the patient's condition permits (8) Inspiration must accompany exercises of the arms that expand the thorax expiration those that compress it (9) A pause of two or three minutes should follow each

individual exercise. (10) Five to ten deep respirations should precede and follow each whole set of exercises.

"Resistive exercises are of special benefit for patients with a somewhat greater cardiac reserve power. Advanced arteriosclerosis, conditions in which acceleration of the blood tends to cause hemorrhage or to increase

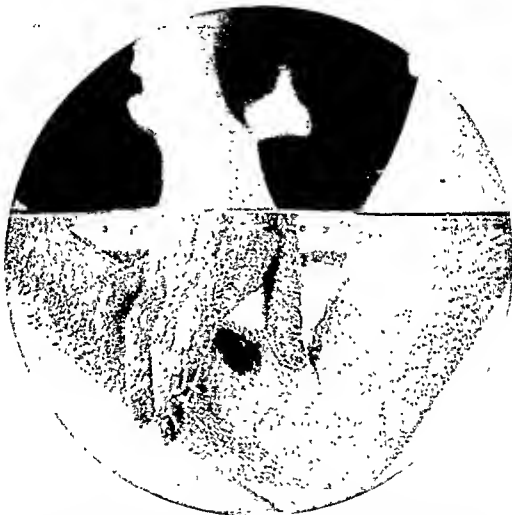


FIGURE 3. Demonstration of CO_2 bubbles, showing manner of collecting on skin

existing hemorrhage, angina pectoris, febrile diseases, profound physical or mental exhaustion and conditions in which rest is essential do not tolerate resistive exercises."

HYDROTHERAPY

The use of natural mineral waters in the treatment of cardiovascular disease was first emphasized by Professor Beneke⁵ of the University of

Marburg in the middle of the last century. It had been his custom to send patients suffering from various rheumatic manifestations to Bad Nauheim during the summer months for baths in the carbon dioxide-impregnated, saline waters flowing there. Many of these patients had

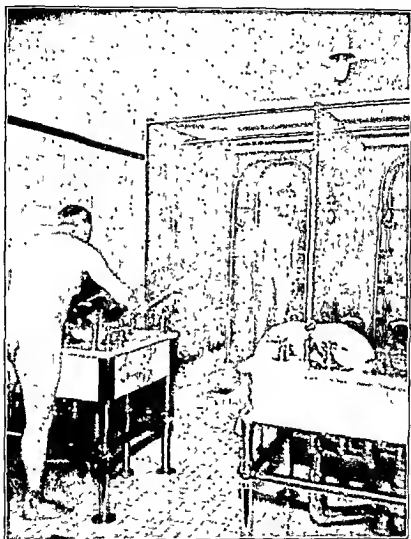


FIGURE 4. Hydrotherapy. The Scotch douche.

complicating heart lesions, and in many instances an improvement in the cardiovascular system was noted by him as a by-product. He thereupon began the cautious use of these baths in patients with various disorders of the heart and circulation and, his results having been satisfactory, Groedel I. Schott and others carried on the work to develop a distin-

guished center for the treatment of these patients with the carbon dioxide baths

Groedel I in particular carried on a long series of detailed observations and established the indications for this work and its technique. It



FIGURE 5. The CO₂ in aeral bath

is noteworthy that during the entire history of this therapy at Bad Nauheim careful study of the patient and detailed regulation and observation of the treatment has been an outstanding feature. Since the origin of this therapy other centers where such waters are available have been developed notably at Royat France Spa Belgium and at Saratoga Springs in this country.

The physiological effect of the carbon dioxide bath has been studied extensively during the past 15 years and considerable information upon the response of the body to its use has accumulated. Professor Franz Groedel⁶ has reviewed the subject recently. Studies by Dr W S McClellan⁷ at the Saratoga Spa are pertinent and we quote from his work. In speaking of the carbon dioxide baths he states: "There are three factors which must be evaluated—first mechanical factors which include the pressure of water on the surface of the body, the buoyancy of the water and the possible massaging effect of the gas bubbles on the skin. The pressure of the water exerted on the outside of the body is of distinct aid in venous circulation as it will compress the veins and increase the pressure within the abdomen. These factors are of value in aiding the return of the blood to the heart."

In the second place there is the influence of heat or the thermic factor. In general a bath at a temperature warmer than the surface of the body will increase the circulation through the skin and add to the work of the heart. A bath at a temperature distinctly lower than the surface of the body will bring about a constriction in the skin circulation and the increased resistance will add to the work of the heart. At the so-called neutral temperature at which the patient does not experience the sensation of heat or cold these thermic factors are at a minimum. In the carbon dioxide bath some of the carbon dioxide will separate from the water and form small bubbles of gas which have a tendency to accumulate over the surface of the body. Some earlier observers considered that the temperature of the gas was in contrast to the temperature of the water and therefore produced a reaction on the skin. There is little evidence at the present time to show that this is a factor of importance in the physiological effects produced.

In the third place there are chemical factors to be considered. As was stated above the carbon dioxide gas accumulates in bubbles all over the surface of the body. Experimental evidence indicates that in solution it is absorbed through the skin and produces distinct effects on the circulation, a detail which will be considered at length later. The salts which are usually chlorides and bicarbonates play a part in producing the buoyancy of the water and also influence the release of the carbon dioxide.

In studying this problem the effects of these factors are manifest in various parts of the body including first the skin and its organs second the deeply seated blood vessels third the respiratory system and fourth the general nervous system

"Pulse Both hot and cold baths increase the rate of the pulse. Clinical observations show that the carbon dioxide bath at neutral temperature will in general lower the pulse rate. This effect of course is more marked the more rapid the rate of the pulse at the beginning of the bath. It is common in many patients with cardiac disturbances to have a rate within the normal range and the change therefore is relatively slight. Also in patients who are easily excitable and nervous this lowering effect may not appear until after a number of baths have been taken. If there is a persistent increase in the rate of the pulse during and after the bath it may be taken as an indication that the bath treatment is too strenuous for the patient and as stated above the duration and the amount of gas in the water should be reduced.

Blood Pressure Many studies of variation in blood pressure during and following the carbon dioxide bath have shown that in general the bath produces a slight elevation in the first minutes generally followed by a slight reduction. Groedel and the author studied this reaction with the use of the Lange Autotonomograph which allows the continuous recording of either the systolic or the diastolic blood pressure. In a small series of normal men they found that the systolic pressure rose slightly and that the diastolic pressure dropped slightly when the patient was lowered into the bath. This reaction was noted in plain water and to a greater degree in the carbon dioxide bath. As a result of these shifts in the systolic and diastolic pressure there was uniformly an increase in the pulse pressure which averaged 15 to 20 mm Hg.

When the patient was taken out of the bath there was a tendency for both the systolic and diastolic pressure to return to the level noted before the bath. The diastolic pressure returned to its original level more slowly than the systolic. In explanation of these findings one must consider that mechanical pressure on the circulatory system plays its part as this factor is present in both the plain water and the carbon dioxide bath. The thermal factor is minimal as both types of baths were given at a neutral temperature. In the carbon dioxide bath there is the additional factor of the carbon dioxide absorbed through the skin during the time

the patient was in the bath. The results noted in the carbon dioxide bath depend on the summation of mechanical and chemical factors.

Venous Circulation As the result of the water pressure exerted on the outside of the body there is a compression of the superficial blood vessels and veins which aids in emptying these vessels. The venous blood is shunted toward the heart. Henderson and his co-workers found that the intramuscular pressure was somewhat higher after the carbon dioxide bath. They interpreted this finding as evidence of increased muscle tonus which they believe is important in maintaining venous blood flow. The weight of the water over the abdomen increases the intraabdominal pressure which aids the return flow from the large veins in this region. It also exerts pressure on the chest and studies of the intrathoracic pressure show that the normal negative pressure in the pleural cavity may be diminished and at times even a positive reading may be obtained. This factor must be considered in the study of the venous circulation as it may hinder the final emptying of the large veins into the right auricle. It also can explain the better results obtained in the half or three quarters bath where a portion or all of the thorax is above the water. It is found necessary to use this type of bath with many circulatory conditions.

The Skin Capillaries The effect of mechanical pressure has been mentioned in the preceding paragraph. In addition there is definite dilatation of these vessels. Microscopic studies of the capillaries following the carbon dioxide bath show an increase in the number of functioning capillaries and in their diameter. It is also a striking clinical observation that there is a hyperemia of the skin in those areas which have been directly exposed to the carbon dioxide water. This hyperemia is sharply demarcated and does not appear in the skin which is above the surface of the water. Physiological studies have shown that carbon dioxide will produce a dilatation of the capillary bed. It is also known that a hot plain water bath will produce a peripheral hyperemia. The carbon dioxide baths are usually given at a neutral point where the thermal effect is not sufficient to produce a dilatation. Therefore it is considered that the influence is due to a direct effect on the vessels of the carbon dioxide or of other substances produced in the skin tissues as a result of the absorption of the carbon dioxide.

The Minute Volume Output of the Heart Results of studies of minute volume output by Kroetz and Wachtel have shown that in both

fresh water baths and in the carbon dioxide baths of Nauheim there is a definite increase in the minute volume output of the heart. In the plain water bath the average increase is approximately 20 to 24 per cent while in the carbon dioxide bath the average increase is from 31 to 34 per cent. They noted that the increased output lasted as long as 40 minutes after the carbon dioxide bath. They also observed the influence of gas baths using air, oxygen and carbon dioxide. They found relatively little increase in the output of the heart with these baths. They conclude that the differences between the plain water and the carbon dioxide baths are not outstanding but in each case the output during the carbon dioxide bath was greater than the output during the plain water bath.

The influence of this factor in the response of the patient to the treatment has not been carefully evaluated or determined. It is considered that there is a reduction in the peripheral resistance due to relaxation of the walls of the arterioles and to muscular relaxation. It is taken as evidence of improvement in the circulation following the use of the carbon dioxide bath.

Effect Upon Respiration The patients usually note that there is an increased effort in breathing when they are under water in the carbonated bath. This increased effort is probably initiated by two factors—first the mechanical pressure on the chest itself may prevent the ease of movement of the muscles of respiration; secondly the absorption of carbon dioxide from the water results in an increase of carbon dioxide in the alveolar air. Through its effect on the carbon dioxide of arterial blood a direct stimulation of the respiratory center occurs initiating increased respiratory effort. Observations of the amount of air breathed during the bath reveal an increase sometimes as high as 30 to 40 per cent in the total volume.

Respiratory Metabolism Careful metabolic observations by Groedel and Wachter have shown the following results. First there is an increase in the amount of carbon dioxide eliminated through the lungs during and following the carbon dioxide bath. This increase may amount to 25 to 35 per cent of the resting elimination. Second they found only a slight increase in the oxygen consumption which would indicate that the carbon dioxide must come from some other source than the oxidative processes of metabolism. Third they noted that the maximum influence on the amount of carbon dioxide eliminated occurred at the end of eight

minutes and that the effect lasted for two hours after the bath. They present this as evidence that carbon dioxide is absorbed through the skin and eliminated through the lungs. They also found that only in the dissolved state or at least in a moist state could the carbon dioxide pass through the skin.

The question is frequently raised as to whether this carbon dioxide could be eliminated from any other supply than from that absorbed through the skin. The fact that the elimination of carbon dioxide following the bath never drops below the normal level is evidence against a blowing off of carbon dioxide or a shift in the hydrogen ion concentration of the blood. One interesting finding of these observations was a respiratory quotient in excess of 1.0, a finding which rarely occurs except in persons who are utilizing carbohydrate exclusively for their metabolic requirements.

"Influence on Skin Physiology" The concept which describes the skin as an organ of internal secretion in which chemical and immunological substances are manufactured is relatively new in the field of medicine. Present day studies are rapidly adding to our knowledge in this field.

The physiological effects of the carbon dioxide bath may in large part depend on the stimulation of an internal secretory function of the skin. It has been shown by physiologists that histaminelike substances may be produced in the skin and also that acetylcholine is produced by the stimulation of the parasympathetic nerve endings. Harpuder was able by using the galvanic current to extract a substance from the skin following its exposure to carbon dioxide waters which biologically acts like histamine. Additional evidence is appearing to support the fact that the production of both a histaminelike substance and acetylcholine is stimulated by the action of the carbon dioxide from the bath.

'Summary' The physiological observations of the influence of carbon dioxide baths show a decrease in the pulse rate, an increase in the pulse pressure dependent mainly on a drop of the diastolic pressure, a better emptying of the venous blood vessels, a hyperemia with increased capillary circulation, a slightly elevated minute volume output of the heart and increase in respiration and the elimination of large quantities of the carbon dioxide through the lungs. The studies of the influence on skin physiology are suggestive but not conclusive.

"Results of Treatment: There is considerable difficulty in judging the response of patients to the use of carbon dioxide baths. The home physician is in some ways best fitted to estimate the response of his patients because he observes their condition during the entire year. The physician who outlines the program at the Spa sees the patient only for the three or four weeks when he is undergoing treatment and at such times as he may return to the Spa for further therapy.

"In a series of patients who received the naturally carbonated mineral water baths, the author and his associates studied the response of pulse and blood pressure in 102 patients. This group included all ages from 16 to 76 years and was made up of 41 men and 61 women. The blood pressure observations were made at the bathing establishment each day before and after the carbon dioxide bath. The blood pressure reading before the bath was taken after the patient rested from 15 to 30 minutes. The authors found a definite response in approximately 30 per cent of the entire group. There were many patients in the series whose blood pressures were normal at the beginning of the treatments. More detailed analyses of those patients whose systolic blood pressure was above 150 mm. Hg at the beginning showed that 52 per cent had a reduction of more than 10 mm. Hg in their systolic pressure at the end of the treatment. In reviewing the case histories of these patients, the authors concluded that the most marked response to treatment was shown by patients with elevated pressure due to nervous disturbances. In those patients with marked essential hypertension or with chronic nephritis with an elevation of the diastolic pressure above 110, relatively little change was observed in their blood pressure as a result of the treatment. It should be stated, however, that many patients in the second group were relieved of headache and symptomatically showed improvement. A study of the variation in pulse rate revealed that the large majority showed a slight reduction after the individual bath. This varied from five to ten beats per minute. When the pulse rate at the end of the treatment was compared with that at the beginning, 28 per cent showed definite reduction in their average pulse rate of more than five beats per minute. It should be stated that at the beginning of this study the majority of the patients had pulse rates varying between 65 and 80 per minute so that one could not expect any striking change in the rate.

"Another study by Comstock, Hunt and Hayden dealt with the results of the treatment in 107 patients who suffered from coronary disease. The course of treatment consisted of the use of the carbonated mineral water baths, rest, regulated activity, and dietary control when needed. Observations of their physical condition at the beginning included in addition to physical examination, roentgen ray plate of the heart, electrocardiogram and vital capacity determination. The patients were observed frequently during the course of treatment and a discussion of their physical condition with them by the physician was a part of the program. At the end of the course of treatment, the observations noted above were repeated. The authors found definite clinical improvement in 96 of the 107 patients. This was noted particularly in the increase in exercise tolerance and diminution in the number and degree of anginal attacks. They found little variation in the size of the heart as judged from their roentgen ray studies. They also noted that in many patients the heart was within normal limits at the beginning of the treatment. The comparison of the electrocardiogram taken at the end with that at the beginning showed 26 cases in which there was evidence of some improvement in the electrocardiographic picture. This improvement was not striking although changes in the T-wave were present in 22 patients. In 15 patients the P-R interval which was either high normal or increased, showed some reduction. There were no significant changes in the Q-R-S complex. They found no significant change in the vital capacity determination after the course of treatment. In a review of 11 patients showing no improvement, the authors state that two did not complete the course of treatment, three had advanced myocardial damage and the rest had other complications which did not respond to treatment. In this group, however, two patients reported improvement after returning home. The authors conclude that this type of treatment is of distinct value for patients suffering from coronary disease. They stress the point that in all circulatory disturbances and particularly in coronary disease it is important to teach the patient regulated living. They point out that several of the patients who showed improvement had previously taken rest cures without the use of carbon dioxide baths with relatively little benefit.

"In evaluating the results of this treatment for patients with circulatory disorders, there is need for more carefully controlled clinical studies of patients who have been treated with carbon dioxide baths. At the

present time there is no ideal test of cardiac function and in these patients the ability to walk or exercise without the production of symptoms is used in judging their clinical gain. In anginal attacks it is striking to note the decrease in the frequency and severity of these attacks. In some patients they will disappear completely. Objective changes as seen in physical examination and in the studies of pulse rate, blood pressure, roentgen ray findings, electrocardiographic tracings, and vital capacity are noted in many patients. However, the subjective improvement and the regularity with which patients return for additional courses of treatment indicate the distinct value of the carbon dioxide bath and the place it should have in treating disorders of the circulation.

The question is frequently asked by physicians: Cannot the results observed be explained entirely on a psychological basis? In answer one must consider the definite physiological observations of the influence of the carbon dioxide bath on the heart and circulation which have been presented in a previous section. One also sees many patients who have had rest cures and psychotherapy without striking benefit and who show both subjective and objective improvement following a course of carbon dioxide baths. The author is a believer in the value of psychotherapy which should be a part of every treatment. The better a patient understands his physical condition the better he is able to adjust his life so that he lives within his physical means. Education of the patient leading to a rational attitude toward his condition must go hand in hand with his treatment. The author recalls a remark by a leading internist of this country when discussing the use of the carbon dioxide bath: I am not so much concerned with the methods by which the results are obtained as I am with the fact that the patients obtain relief from their ailment.

OCCUPATIONAL THERAPY

To be able to create something to justify the fact of one's existence by useful production is a basic human desire. It purveys too ego gratification and can be made especially useful in building up the morale of those more seriously ill with cardiovascular disease. Even more important in many instances is the opportunity to train the individual in an occupation suitable to his physical capacity and one that may be made gainful. This applies especially to patients in Classes II A and II B and calls for individualization and ingenuity. Many can undertake vocational

training others are restricted to such pursuits as cabinetwork bookbinding leather tooling weaving basketry and toy manufacture

For the patient whose condition necessitates bed rest future vocation or recompense for articles sold is a secondary consideration which cannot be permitted to interfere with the need for physical and mental rest. There are two groups which fall under Class III—those with active infections damaging the heart and those with hearts already damaged and which have failed because of too heavy a circulatory burden. When such patients progress to Classes II B II A and Class I vocational training can become of importance but occupational therapy during the period of bed rest may open the door to it.

For patients confined to bed it is obvious that only bed occupation may be utilized. A bed table with hinged supports at either end is made easily and upon this many things may be undertaken. Painting for instance or the making of a scrapbook. For a man forced to lie upon his back braid weaving upon a suspended frame is feasible as is cord work which involves knotting and tying. Basketry may be done in a recumbent or semirecumbent position and affords much interest and quick results. For women needlecraft is of most value. Whatever the undertaking the prevention of physical and mental weariness must be an important consideration. (See Chapter XXXIII.)

ETIOLOGY OF CARDIOVASCULAR DISEASE AND INDICATIONS FOR PHYSICAL THERAPY

The etiologic factors in cardiovascular disease include

Congenital Cardiovascular Defects. Those individuals suffering from congenital cardiovascular defects who reach maturity almost without exception suffer only from such slight defect as a small opening in the interventricular septum and are for clinical purposes relatively normal. By far the greater majority of these patients however have severe defects and die during the earlier years of life. Any physical therapy limits itself of necessity to the myocardial status of the individual and at most would consist of gentle voluntary movements or better of some form of passive exercise such as mechanotherapy or massage. This latter understandingly given is probably the one most useful procedure. Ultraviolet radiation is of possible help and occupational therapy is highly indicated.

Rheumatic Heart Disease The concept of rheumatic fever in any of its several manifestations presupposes heart damage or potential heart damage. During the active stages of the disease there is no field for physical therapy but during the tedious days of convalescence much may be done to improve the physical status of the patient and to bolster his morale.

Again the procedure used must take into consideration the whole clinical picture. Massage starting with effleurage and as circumstance permits more active forms such as gentle kneading and vibration may be permitted. Following this if no untoward event intervenes passive movements and then active ones follow. Again heliotherapy may be used and suitable occupational therapy is especially indicated.

The question of hydrotherapy such as the carbon dioxide bath is given it a spa is not to be considered in the opinion of the author except in those patients who have manifested no activity for a long period of time. When properly given these baths combined with a well planned regime can do much to put off the inevitable onset of congestive failure. The baths are of material use too in the earlier stages of such failure in combination with a regime of rest and suitable exercise.

Acute and Subacute Bacterial Endocarditis Physical therapy is contraindicated in these instances.

Cardiovascular Syphilis Because of earlier diagnosis and more competent treatment the outlook in cardiovascular syphilis has improved modestly during the past few years. The prospect of an occasional sudden death in this disease particularly must be kept constantly in mind and any form of physical therapy is to be undertaken with consideration. The procedures employed depend as has been mentioned several times upon a careful estimate of the myocardial status. Passive or active exercises, resisted movements, massage, perhaps a regime at a suitable spa are permissible and occasionally helpful.

Other Infections (Scarlet Fever, Diphtheria) The considerations which hold for patients suffering from rheumatic heart disease are applicable in these instances.

Thyrototoxic Cardiovascular Disease Well-chosen procedures aimed at the restoration of myocardial reserve are a useful adjunct to postoperative convalescent cure. Again these procedures must be suited to the

individual circumstance. In later convalescence a few weeks of régime and a suitable spa may be of considerable benefit.

The Myxedematous Heart As an adjunct to specific therapy well chosen physical therapy can be of real service. Massage, hydrotherapy and spa régime are well suited.

Heart and Deficiency Disease (The Beriberi Heart) An increasing number of patients with cardiovascular disability who have no etiological factors other than excessive alcohol and inadequate diet are being seen. The disability varies in degrees from tachycardia to very evident congestive failure and responds promptly to vitamin B₁ in large dosage, rest, abstinence and suitable dietary. During the convalescent state massage, exercise and hydrotherapy are most useful. Spa therapy for the rehabilitation of the physical status has proven of real service.

Degenerative Heart Disease Including Hypertensive Heart Disease, Coronary Artery Disease and Coronary Thrombosis In the author's experience there is no group of sufferers from heart disease that can receive more benefit from the various forms of physical therapy than these. The problem presents itself as one primarily of securing the maximum of myocardial integrity and thereafter of its maintenance during the declining years of life. This type of patient does particularly well under spa régime. Sequestered life, large increments of rest, supervised exercise and suitable forms of hydrotherapy work together for the well being of the patient. There is much, however, that may be accomplished at home to slow the tempo of life, to teach routine rest and by means of massage and other suitable forms of exercise to maintain a good physical status.

The carbon dioxide bath has given excellent results in the amelioration of the discomforts of coronary insufficiency. Although satisfactory experimental evidence is not yet available, it is believed that an increase in coronary flow is produced by these baths. There occurs a slowing of the pulse rate and often a simultaneous fall in blood pressure. It has been demonstrated that the minute volume output of the heart is increased. Alexander Lambert⁸ has evaluated the rather extensive experimental work done and has postulated a tenable theory based upon the action of carbon dioxide on the autonomic nervous system.

Physical therapy plays an important part in the rehabilitation of the convalescent from coronary thrombosis. Any procedure is contraindicated

until thorough healing of the infarct is complete. In a study of the speed of healing of myocardial infarction by Mallory White and Salcedo-Solgar⁹ it was found that small infarcts are almost completely healed after five weeks and that large ones are completely healed or undergo no further discernible change after two months. Certainly then if the myocardial status otherwise permits light massage and passive movements may be begun safely by the tenth week. The progression from this point onward is gauged by the reaction of the patient. At the end of four to six months many patients are benefited by a stay of several weeks at a suitable spa.

Pulmonary Heart Disease. Prior to the stage of congestive failure the treatment of cor pulmonale is primarily that of the causative lung factor and when possible residence in an equable dry climate is of major importance. Physical therapy during the stage of congestive failure is governed by principles similar to those of congestive failure of any other form of heart disease.

Neurocirculatory Asthenia and the Cardiac Neuroses. *This group represents one that is greatly benefited and often cured by means of physical therapy in conjunction with other forms of treatment. They do particularly well under a spa regime.*

SOURCES AVAILABLE FOR ADMINISTRATION OF PHYSICAL THERAPY

Departments of physical therapy have been developed in most of the larger medical centers and not infrequently in the smaller ones. Many physicians have facilities of greater or lesser extent in their offices. However in the instance of cardiovascular disease the writer much doubts that any good consonant with time and energy spent can result from a daily trip to the hospital or the doctor's office. These procedures for the most part find their greatest usefulness in heart disease as a part of an organized regime at a sanatorium or at a spa and undertaken over a period of weeks.

The better known cures of Europe will be found most satisfactory particularly Bad Nauheim in Germany and Royat in France. In this country excellent work is being done in cardiovascular disease at Clifton Springs, Glen Springs and at Saratoga Springs in New York State.

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CHAPTER XLIII

NORMAL BLOOD PRESSURE AND ITS PHYSIOLOGIC VARIATIONS

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Introduction: In spite of a large amount of work which has already been done on blood pressure, there is still great need for information in regard to standards of normal and physiologic variations from normal.

As so often happens in medicine, when physicians first discovered hypertension, they immediately devoted most of their efforts to curing it, and but few attempts were made to determine when a given pressure represents disease and when it is only a physiologic variation from the average. Even today there is great need for a more careful biometric and anthropologic approach to the problem.

The records made in the early years are of little value today, because they were made with all sorts of instruments and with methods different from those which are now commonly used. Fortunately, with the passage of time, a considerable degree of standardization has been achieved, both as regards the instrument and the method. Today practically everyone uses a cuff of standard width and a manometer which is calibrated in terms of millimeters of mercury. For careful scientific work, the mercury instrument is to be preferred, because there must always be a little fear that an aneroid type of manometer is out of adjustment.

In the early days, blood pressures were taken by the palpatory method, but in more recent years most observers have been listening for the sounds and have been getting readings about 5 mm. higher than those obtained by palpation. Even today, when studying diastolic pressures, the statistician must be careful to learn what method was used in determining the end point. Most observers take as a criterion of the diastolic pressure the beginning of the fourth Korotkov sound.

But even when two observers are using standard instruments and the same technic in measurement, they tend to differ markedly in their readings, and this for a number of reasons. Some measure carelessly; they

Pioneers in the Advance of the Knowledge of Diseases of the Heart by the Aid of Instruments of Precision



Rev. Stephen Hales (1723) in his parsonage at Teddington on the Thames using an old mare carried out the first experiments on blood pressure. Later he made additional observations on blood velocity and cardiac capacity and published the whole in *Statistical Essays* in 1733 destined to become the only contribution to the subject for 100 years.



Bowditch in 1871 established the first physiological laboratory in America and made the mural investigation of the all or nothing principle of contraction in heart muscle.



Einthoven made possible the development of modern electrocardiography by the introduction of the delicate string galvanometer for measuring the cardiac action currents of Waller. The records he obtained of the heartbeat he named *electrocardiograms*.



Sir Thomas Lewis developing the method of electrocardiography in the present century has succeeded in bringing complete order out of the chaotic state of our knowledge of the cardiac arrhythmias.



Mackenzie perfected and used the polygraph in the study of the arrhythmias and was the first to make simultaneous records of the arterial and venous pulses. His pulse tracings examples of skill and patience led him close to the solution of all of the cardiac irregularities.

allow the column of mercury to drop rapidly, and they read to the nearest multiple of ten on the scale. Others have unusually acute or unusually poor hearing, and this makes a difference. But even when the oscillations of the manometer are recorded graphically, as they are with the Erlanger and the Tykos instruments, there is still much likelihood of differences of opinion, as was shown by Kilgore⁵⁶ many years ago. He sent duplicate sets of records obtained with an Erlanger instrument to a number of the leading physiologists and cardiologists in the United States; he asked them to mark points of systolic and diastolic pressure, and he received conflicting reports. For further discussion of some of these problems the student should turn to papers by Warfield⁵⁷ Judson and Nicholson,⁴⁸ Schrumph and Zabel,⁸¹ MacWilliam⁶⁴ and Norris, Bazett and McMillan⁷⁴.

Carelessness, of course, is one of the greatest causes of obtaining poor results, and the statistician will always want to know how and by whom the records under consideration were taken. Furthermore, he must be sure that they were taken without bias. Unfortunately, many of the figures supplied by insurance companies are invalidated by this defect. Any physician who has ever done any examining for insurance companies knows that unless he is willing frequently to read low, the agent who patronizes him will soon seek elsewhere for someone who is more compliant. This is not a pleasant statement to have to make, but the fact must be faced by all who would study blood pressure with statistical methods.

In many ways, it would seem as if blood pressure ought to be taken under basal conditions. Addis¹ has shown that when the readings are made while the man or woman is still resting in bed before breakfast the figures obtained are much lower and more constant than those obtained later in the day. The difficulty, of course, is that the method is not practical for everyday use, and it is questionable if the results obtained would warrant the extra inconvenience to the physician and the extra expense to the patient. Perhaps what the physician needs most to know is not the basal pressure, but the pressure that is present during the many hours of the day in which the patient is subject to the wear and tear of work, emotion, and fatigue.

It is probable also that much information of value could be secured by comparing the basal and the midday pressures. As Brown¹¹ and his

students have shown, the only way in which to learn all the facts about blood pressure is to make readings at frequent intervals during the day and night, and daily over a period of at least a week. Anyone who has ever seen a record made in this way will realize how erroneous those conclusions are likely to be which are drawn from a few readings taken haphazardly in morning or afternoon, on Monday or on Saturday.

Let it be supposed that a physician has found on Monday morning in a certain patient a systolic pressure of 200 mm of mercury. He gives a drug for example, sodium nitrite, and asks the patient to return the next afternoon. He then finds a pressure of 170 mm and congratulates himself on having obtained a good therapeutic result. But if the patient had failed to take the medicine, the reading might still have been 170 mm because this is perhaps the normal afternoon pressure for this particular patient. As Brown has shown it is almost impossible in any one case to judge of the value of some form of treatment until the cycle of normal changes in blood pressure in the particular man or woman is first studied.

As everyone knows there are many more or less physiologic factors which are capable of influencing blood pressure and which should be taken into account in all determinations especially in those that are to be used for statistical purposes or for comparison with those that have been taken by observers elsewhere. The most important of these factors will now be taken up *seriatim*.

The joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland* relative to the standardization of blood pressure are worthy of quotation here.

STANDARDIZATION OF BLOOD PRESSURE DETERMINATIONS

1 **Blood Pressure Equipment** The blood pressure equipment to be used whether mercurial or aneroid should be in good condition and calibrated at yearly intervals—more often if defects are suspected. (Mercurial preferred—British Committee.)

2 **The Patient** The patient should be comfortably seated (or lying—British Committee) with the arms slightly flexed and the whole forearm supported at heart level on a smooth surface. If readings are taken in

* American Heart Journal 18:93 (July) 1939

any other position, a notation of that fact should be made. The patient should be allowed time to recover from any recent exercise or excitement. There should be no constriction of the arm by clothes, etc.

3. Position and Method of Application of the Cuff: A standard-sized cuff containing a rubber bag 12 to 13 cm in width should be used. A completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about one inch above the antecubital space and with the rubber bag applied over the inner aspect of the arm. The cuff should be of such a type and applied in such a manner that inflation causes neither bulging nor displacement.

4. Significance of Palpatory and Auscultatory Levels: In all cases palpation should be used as a check on auscultatory readings. The pressure in the cuff should be quickly increased in steps of 10 mm Hg until the radial pulse disappears, and then allowed to fall rapidly. If the radial pulse returns at a higher level than that at which the first sound is heard, the palpatory reading should be accepted as the systolic pressure, otherwise the auscultatory reading should be accepted.

5. Position and Method of Application of Stethoscope. The stethoscope should be placed over the previously palpated brachial artery in the antecubital space, not in contact with the cuff. No opening should exist between the lip of the stethoscope and the skin; this should be accomplished with the minimum of pressure possible. The hand may be pronated or supinated, depending on which position yields the clearest brachial pulse sounds.

6. Determination of the Systolic Pressure: The cuff should be rapidly inflated to a pressure about 30 mm above the level at which the radial pulse can be palpated. The cuff should then be deflated at a rate of 2 to 3 mm Hg per second. The level at which the first sound regularly appears should be considered the systolic pressure, unless, as pointed out above, the palpatory level is higher, in which event the palpatory level should be accepted. This should be noted.

7. Determination of the Diastolic Pressure and the Pulse Pressure: With continued deflation of the cuff, the point at which the sounds suddenly become dull and muffled should be known as the diastolic pressure. If there is a difference between that point and the level at which the sounds completely disappear, the American Committee recommends that

the latter reading should be regarded also as the diastolic pressure. This should then be recorded in the following form RT* (or LT†) 140/80 70 or 140/70 0. If these two levels are identical the blood pressure should be recorded as follows 140/70 70. The cuff should be completely deflated before any further determinations are made.

The British Committee believes that except in aortic regurgitation it is nearly always possible to decide the point at which the change comes and that this is the only reading which should be recorded.

Explanatory Comments. In addition to the above specific recommendations the Committees believe that certain other factors should be taken into consideration by the physician who makes blood pressure determinations.

The relative merits of various types of sphygmomanometers have been the subject of numerous reports. In the opinion of the joint Committees mercurial and aneroid types of apparatus are capable of correct readings if they are in good condition and both types of equipment may produce inaccurate findings if not in good condition. This factor is often overlooked in the case of the mercury manometer which should be checked at intervals as to the following points:

1. The level of the mercury at rest should be exactly at the zero mark. If some of the mercury has leaked out this will not be the case. The missing mercury should be replaced.

2. If the small air vent at the top of the glass tubing becomes clogged a definite lag may be produced the mercury column may not register the pressure in the bag and the readings will therefore be incorrect.

3. The apparatus must be on a level surface since tilting of the manometer will result in incorrect readings. It should also be level with the observer's eyes.

A yearly calibration of the aneroid type of instrument against a U tube standard is recommended. This is particularly advisable for the older instruments in which a sharp blow or fall may cause inaccuracies due to resultant changes in the aneroid diaphragm. The needle should stand at zero when the apparatus is completely deflated and move immediately when the inflation begins. Monometers which have a stop pin at zero or those which have a rotatable dial permitting the user to set

* RT = right arm
† LT = left arm

the zero mark anywhere are not recommended since a satisfactory check with instruments of this type is impossible.

In both types of equipment the valves of the instrument, including those of the rubber bulb should be competent and function smoothly. The entire system including the pressure rubber tubing and rubber bag must be free from leakage and must be kept in good condition. It is recommended that the instrument to be used be checked at yearly intervals against a machine known to be in perfect condition. More frequent checks should be made if the accuracy of the instrument is in doubt. The rubber cuffs should be 12 to 13 cm wide and 23 cm long. The cloth covering should be of inextensible material of such a nature that even pressure is exerted throughout the width of the cuff; it should extend as a band 15 cm wide for 60 cm beyond the edge of the rubber cuff and then taper gradually for an additional 30 cm. New types of cuff using a zipper mechanism or hooks on a rib extending the width of the cuff appeared to be more satisfactory than the long tapering cuff end. If bulging occurs above and below the band the reading may not be accurate.

A special cuff should be used to measure blood pressure in the leg. The rubber bag should be 15 cm wide and its covering 17 cm wide and 30 cm longer than in the case of the armlet (total 120 cm). For children cuffs of the following widths have been suggested: Under eight years less than 9 cm; under four years less than 6 cm; newborn babies less than $2\frac{1}{2}$ cm. The limited work done in this field does not warrant a definite recommendation at this time.

The American Committee selected the sitting position as the preferable one because of the fact that it simplifies the taking of large numbers of blood pressure readings. It is true that many patients are bedridden but in most instances they may be propped up into a sitting position without causing more than transitory disturbances in the circulation and when this is impossible it is suggested that a notation be made as to the position in which the blood pressure is taken. The British Committee did not think that there was any significant difference between the sitting and lying positions. For blood pressure readings in the thighs the stethoscope bell should be placed over the popliteal artery with the patient prone.

Certain physical and psychologic factors should be considered. Inquiry should be made as to the patient's activity just before the examination. Exercise and meals affect the blood pressure. A rest period of from 10 to 15 minutes prior to the making of the observations will eliminate or minimize certain of these factors. It is important that the physician evaluate the degree of stress or emotional crises through which the patient may be passing. The first reading taken by a physician is often much higher than later ones due to apprehension and nervousness on the part of the patient. It is often wise therefore to avoid conclusions regarding the blood pressure level of an individual until several readings have been made on successive visits. This is especially important with hypertensive and hyperthyroid patients. Any evidence of apprehension or of undue concern on the part of the physician may alarm the patient and increase the pressure.

There are variations in the blood pressure level of certain individuals in the course of a day. It is therefore suggested that for careful records the time of the day should be noted and if the patient is being carefully followed with reference to the blood pressure level the observations should be made at essentially the same time and in the same relationship to meals, sleep, exercise and other similar factors.

The term "points" is suggested for use in reference to diastolic pressure since the word "phase" formerly used implies a measure of time interval whereas in reality the fourth and fifth points are the exact levels at which change is made from one phase to the next. Detailed discussion of the second and third phases is not pertinent to this report since those phases are of little if any practical importance and tend to confuse the issue at hand. It should be clearly recognized that a single figure for systolic or diastolic pressure apparently does not represent actual pressure within from 5 to 10 mm. of mercury. If the physician wishes to minimize the sources of error several blood pressure readings should be made, the highest and lowest being recorded. Although an average of the series of readings might be recorded, this would not have the same significance in instances of cardiac irregularity.

The determination of blood pressure in arrhythmias is unsatisfactory at best when made with the apparatus under discussion. With premature beats the higher systolic pressure of the beats that terminate compensatory pauses should be ignored. With auricular fibrillation both diastolic

and systolic readings should be recorded as approximate only. It is suggested that in this condition the average of a series of readings for the appearance of the first sound be noted as the systolic pressure, and that similar averages for the fourth and fifth points be recorded as the diastolic pressure. The diagnosis if not stated elsewhere on the patient's chart should be noted with the blood pressure recording. In aortic regurgitation with a collapsing pulse the diastolic end point is sometimes marked by a less obvious change in the quality of the sounds than normally. This change may be difficult to appreciate.

Alternation of the pulse during blood pressure determinations may indicate left ventricular weakness.

It is suggested that when especially careful studies of the blood pressure are to be made the use of basal blood pressure conditions should be considered. A preparation similar to that used prior to measuring the basal metabolic rate is recommended. Such a basal blood pressure determination should be made 10 to 12 hours after a meal (preferably in the morning) after the patient has rested for 30 minutes in a comfortably warm room. The patient should be mentally as well as physically at ease. This procedure would be most useful in experimental studies in which an accurate standard level is desired. Objections to its use in general practice are obvious.

When auscultatory methods alone are used the actual blood pressure level may be definitely higher than the level at which the first sounds are detected. Under these circumstances the palpatory reading will be the more nearly correct of the two. If both palpatory and auscultatory methods are used as recommended this error will be detected.

In occasional instances the usual sounds are heard over the brachial artery at a fairly high level; as the pressure in the cuff is reduced the sounds completely disappear only to reappear at a distinctly lower level. This zone of silence is known as the auscultatory gap. Its existence is obviously important inasmuch as it is possible in such patients to inflate the cuff only to the level of the auscultatory gap and to record the systolic pressure at the level where sounds are first heard which may actually be 40 or 50 mm. below the true systolic level.

The importance of avoiding unnecessary venous congestion should be recognized. This can be minimized by making certain that there are no

constricting bands on the patient's arm and that the pressure cuff is not kept inflated longer than absolutely necessary to make the blood pressure reading. Decompression should be at the rate of approximately 2 to 3 mm Hg per second. After making a reading the cuff pressure should be reduced to zero long enough to allow the veins to empty before another determination is started.

It is suggested that on the first examination of the patient the blood pressure be taken in both arms since the two may not be the same. If the patient is followed for a period of time this procedure might wisely be repeated at stated intervals of every few months and at other times if indicated by developments. In the presence of unexplained high pressure in the brachial arteries it is suggested that the blood pressure in the legs be taken also. By this procedure conditions such as coarctation of the aorta may be detected.

If the variations in blood pressure which occur with respiration are considerable this factor may be eliminated by taking a reading while the patient holds his breath at midrespiration but this must be for only a short interval or abnormal blood pressure readings due to asphyxia and other factors will result.

Certain factors inherent in the physician such as variations in accuracy of hearing must be recognized as important. A physician who is aware that his hearing has become impaired should use a stethoscope in which sound is amplified to a considerable extent and in the event of marked deafness electrically amplified or other mechanical devices should be utilized. It is thought inadvisable at this time to make recommendations regarding automatically recording blood pressure equipment.

The combined use of the auscultatory and palpatory methods as described herein will yield routine data that are as reliable as those given by any other method. Under exceptional circumstances as when the pulse is too feeble to produce sounds or too irregular for averaging recording methods may become necessary. Those contemplating the use of graphic methods should first ascertain through reliable sources whether they will subserve the ends in mind.

The recommendation of a standard procedure as outlined by the Committees is not intended to discourage initiative when indicated in special situations.

PHYSIOLOGIC VARIATIONS OF NORMAL BLOOD PRESSURE

1 Posture Sewall⁸⁵ and Christ³⁰ studied the blood pressures of normal persons as they were moved passively from the recumbent to the erect position and found no significant change in the systolic readings the diastolic pressure rose on an average about 12 mm. In Cruickshank's²⁰ group of subjects the average pressure with the patients recumbent was 112 mm systolic and 78 mm diastolic and with them sitting 103 mm systolic and 78 mm diastolic.

Erlanger and Hooker²⁴ found that when their subjects stood up after lying down some showed an increase while others showed a decrease in systolic blood pressure. Lee⁶⁰ who studied the pressures of 662 men found 85 in whom the blood pressure standing was in excess of 140 when the 662 men lay down there were only 31 with a pressure more than 140 mm. The change in posture was apparently in active one, i. e. carried out by the person himself unfortunately Lee did not state in which position the blood pressure was taken first. His data lend some support to the view that systolic blood pressure is higher when the man or woman is standing.

Mortensen⁷¹ studied the blood pressure of 90 normal girls first recumbent and then after they had been tilted into the erect position. The change produced a slight fall in the systolic and a greater rise in the diastolic pressure. Schneider and Truesdell⁸⁰ studied 2000 aviators whose average age was 25 years. In the recumbent position the mean systolic pressure was 118.0 ± 0.2 mm after they had stood up it was 120.3 ± 0.2 mm. At the same time the diastolic pressure rose usually about 8 mm. Schneider and Truesdell quoted the results of four investigators three of whom found an increase in the recumbent systolic pressure as compared with the standing or sitting pressure and one who found lower pressures in the recumbent position. Sewall⁸⁵ concluded after an analysis of several hundred observations that the active change from the recumbent to the standing position will always bring about a rise in diastolic pressure. From this work it seems fairly obvious that when the subject of the experiment is moved passively the change from the recumbent to the erect posture does not change the systolic pressure very much; when however the change of posture is an active one brought about by the subject's own muscles the pressure is raised in both types

of experiment *i.e.*, with passive and active change of position the diastolic pressure rises

2 Sleep Lowering of blood pressure during sleep has been demonstrated by Landis⁵⁷ Brooks and Carroll¹⁰ Brush and Fayerweather,¹² Campbell and Blankenhorn¹⁶ Mueller and Brown⁷² Tarchanoff⁹³ Muller⁷³ Howell⁴² and Katsch and Pansdorf⁵² MacWilliam⁶³ believed that restful and sound sleep lowered blood pressure while unsound sleep caused by unpleasant dreams increased it. He believed that such rises in pressure might account for many of the vascular accidents which occur during the night. He found two cases in which during sleep the systolic pressure rose 40 and 70 mm respectively. Hill^{37, 38} concluded that blood pressure falls during sleep only as much as it falls when a man lies awake in bed. Brush and Fayerweather¹² found that it falls during the first hours of sleep only to rise again gradually so that on awakening it is higher than in the evening before. Campbell and Blankenhorn¹⁶ found the pressure at its lowest point in the fourth hour of sleep and believed that this low level was maintained for the rest of the night. Brooks and Carroll¹⁰ found the lowest pressure after the first one or two hours of sleep. The pressure on awaking was lower than it was during the previous afternoon and it did not return to this high level until late the next afternoon. So far as they could see it did not make any difference whether the man or woman slept during the day or at night. Landis⁵⁷ found pronounced rhythmic changes in blood pressure during sleep. Mueller and Brown⁷² found the lowest pressure between the hours of 3 and 4 in the morning after which there was a gradual return to the usual morning level.

On summing up these studies it appears that blood pressure normally falls during restful sleep. So far observers do not agree as to the form of the normal curve of hourly fluctuation. *It is probable that sleep of itself does not influence the blood pressure only in so much as it produces complete rest and relaxation.*

3 Diurnal Variations Mueller and Brown,⁷² who took blood pressure readings every hour of the day and night in a group of 26 normal persons found a gradual rise during the day and a fall during the night. The high point in the curve came usually about 6 or 7 P.M. A study of figures 3 and 4 in their paper shows that there are three daily peaks in figure 3 they come at 9 A.M. and 11 and 7 P.M. in figure 4 they came

at noon and at 3 and 7 P. M. These peaks can hardly be ascribed to the taking of food.

Weiss⁹⁸ found systolic readings at night 20 mm. higher than those made at 9 A. M., and Zadek¹⁰¹ found a midafternoon rise independent of the midday meal. Hill³⁷⁻³⁸ studying his own blood pressure found it higher after a day's work than in the morning. Brown¹¹ trained a young man with severe hypertension to measure his own blood pressure several times a day for months and years. The curves so obtained showed a definite daily cycle with the pressure lower in the morning than in the afternoon. In addition there was a striking weekly cycle with a gradual rise from Thursday to Sunday and then a fall again until Wednesday. The rise from Thursday to Saturday might easily be ascribed to increasing fatigue, but the high point on Sunday was hard to understand until the man, a bachelor and a steamfitter, explained that on Saturday and Sunday his routine was disturbed, he missed the tranquilizing effect of work and in consequence became restless and irritable.

Faught²⁶ found a gradual rise in blood pressure during the day. Hensen³⁶ who studied a healthy girl who remained in bed for 19 days found that the evening systolic pressure exceeded the early morning pressure by from 5 to 15 mm. Sigler⁸⁷ found hourly variations in blood pressure independent of psychic effects, meals, posture, etc. Weyss and Lutz⁹⁰ found similar variations which they thought were due largely to the taking of food. Jellinek⁴⁶ studied two healthy soldiers on sentry duty and found the systolic pressure somewhat lower in the evening than in the morning.

4. **Emotions.** Emotions tend to raise blood pressure, as has been shown by Cannon¹⁷, Schrumph⁸², Marston⁶⁵⁻⁶⁶, Cabot¹⁴, Tixier⁹⁵, Addis¹, O'Hare⁷⁵, Kilborn⁵⁵, Diehl and Lees²¹, Scott⁸³, Dumais, Lamache and Dubar²³, Tigerstedt⁹⁴ and Crollman³². A rise can be caused by feelings of pleasure, anger, fright, apprehension, excitement, and general nervousness. Marston⁶⁷ found a fall in blood pressure resulting from feelings of compliance and submission. Scott⁸³ found no correlation between the strength of the emotion as judged by the subject and the amount of change in pressure. Landis and Gillette⁵⁸⁻⁵⁹ who studied the blood pressure of persons being questioned, concluded that the slight, usually 3 mm. rise observed sometimes during attempts at deception were too small to have diagnostic value.

The effect of emotion on blood pressure can be seen in the well known fact that the reading is likely to be higher at the first interview than at subsequent ones. Thus Diehl and Lees²¹ studied 100 University fresh men who had been judged to be normal on the basis of a physical examination made shortly after matriculation. Taking the first readings made on each man the mean systolic blood pressure was found to be 118.7 ± 0.7 . Subsequent readings were then made every five minutes for an hour. After the first five minutes there was a mean fall in pressure of 2.9 ± 0.9 mm. After the second five minutes there was another mean fall of 3.7 ± 1.0 mm. After another five minutes the readings became fairly stable with a mean of 111.0 mm.

Gallavardin and Haour²⁹ in a study of 100 persons found a systolic blood pressure from 25 to 35 mm higher at the first reading than it was later when the subjects were accustomed to the procedure. O'Hare⁷⁵ found systolic blood pressures 21 mm and diastolic pressures 10 mm higher on the first measurement than on later ones when the subjects of the observations had been allowed to rest for from 5 to 70 minutes. Sigler⁸⁷ attempted to eliminate psychic influences by isolating the examining room as far as possible from outside influences and by allowing the patient to rest from three to five minutes. He made blood pressure determinations every minute for from 10 to 25 minutes. His study of 72 normal persons showed practically no variation of pressure in 50 but variations of from 10 to 30 mm in the other 22. He did not state whether these variations represented increases or decreases in the level of blood pressure. Alvarez³ who compared blood pressure readings made on 100 office patients on the occasions of the first and second visits found differences sometimes as high as 40 mm. When he compared the sums of the two measurements he found them practically identical.

There is no doubt that in some persons blood pressure is much more variable than in others and this difference may some day be found to have great significance. Allen, Bowing and Rowntree² showed that there is almost always a marked fall in blood pressure when a patient is put to bed and kept there for a few days. *For this reason it is impossible to judge of the effect of any therapeutic measure until the pressure has become stable at the new, resting level. It is unfortunate that most of the physicians who in the past have attempted to evaluate methods of treating patients with hypertension have been unaware of this fact. It should be*

obvious from all this that a single measurement of blood pressure, especially in a person who is anxious or emotionally unstable, can have little value

5 Muscular Effort Cannon¹⁷ showed that great muscular effort increases the blood pressure. He believed this to be due to the forcing of blood from the abdominal vessels into other parts of the body. During effort the diaphragm and muscles of the abdominal wall are probably contracted so as to stiffen the trunk and thus offer support for the arms. Cook and Briggs¹⁸ found an increase in the blood pressure of infants during nursing. Erlanger and Hooker²⁴ noticed that moderate exercise will sometimes diminish diastolic pressure and severe exercise will increase it. McCurdy⁶⁹ concluded that muscular effort can increase systolic pressure by as much as 70 mm. and Schneider and Truesdell⁸⁰ found that it can increase also the diastolic pressure. Addis¹ found during study of ten normal persons that after short periods of exercise the mean systolic blood pressure rose from 121 to 137 mm. and after longer periods it rose to 168 mm. Systolic pressure appears then to be increased by muscular effort of any degree; diastolic blood pressure on the other hand is decreased by moderate exercise and increased by severe muscular effort.

6 Meals Increased blood pressure during or shortly after eating has been noted by Taught²¹, Loeper⁶², Cook and Briggs¹⁸, Gumprecht³³, Sommerfeld⁸⁸, Hayashi³⁵, Weiss⁹⁸, Jellinek⁴⁶, Zadel¹⁰¹ and May⁶⁸. Weiss⁹⁸ however found decreases after breakfast and luncheon and a rise after the evening meal. Erlanger and Hooker²⁴ found a similar variable response to meals but thought there was a fairly constant tendency to an increase in pulse pressure. May⁶⁸ believed that a postprandial increase in blood pressure is to be found only in health; during illness there is likely to be a decrease in the level of pressure. Jewnary⁴⁵ found a rise of 5 mm. in the systolic pressure and an equal fall in the diastolic pressure following dinner and supper. Maximowitsch and Rieder⁶⁷ and Karrenstein⁵¹ found an increase in blood pressure after the drinking of fluids.

7 Difference in Blood Pressure in the Two Arms Kay and Gardner⁵³ had their attention directed to differences in pressure in the two arms by the discovery of a person with a reading of 130 mm. systolic pressure in the left arm and 165 mm. in the right. They studied a group

of 125 persons and found 25 with significant differences between the measurements in the two arms. The difference was at times as great as 40 mm in the systolic pressure and 20 mm in the diastolic pressure. Stephens⁸⁹ found that pressures tend to be on the average from 3 to 4 mm higher in the right arm than in the left arm. Bodenshtab⁹ examined 100 patients and found ten with different systolic and four with different diastolic pressure readings in the two arms. In these persons neither arm showed a consistently higher pressure. Unfortunately in all but two cases he failed to state whether the first reading was the higher, a fact of great importance (Diehl and Lees²¹).

8 **Position of the Arm** Kahn⁴⁹ found on studying 27 normal persons that there was an average fall of 55 mm in the systolic pressure when he raised the arm from the dependent to the vertical position.

9 **Menstruation and Pregnancy** Studies of Griffith and his associates³¹ on five subjects showed that the systolic pressure (standing) is lowest during the latter part of the intermenstrual period. It tended to be highest during the week of menstruation. The work of Moore and Cooper⁷⁰ showed that menstruation does not seem to affect the normal weekly rhythmic cycle of change in systolic pressure.

Stieglitz⁹⁰ found a gradual rise in arterial tension during the final month of pregnancy. There was a fall immediately after parturition and a rise again with the onset of lactation. Cornell¹⁹ who studied 1000 women concluded that in the largest most normal group the pressure was lower throughout pregnancy than in normal nonpregnant women. Much of the literature on the subject is summarized in his paper. Seward and Seward⁸⁶ found that pregnancy was accompanied by an early rise and later fall in the systolic blood pressure.

10 **Constipation** The study made by Alvarez, McCalla and Zimmermann⁵ on office patients showed that constipation has little if any effect on blood pressure. No significant difference was found between the mean pressures of constipated and nonconstipated men. In women constipation seemed slightly to lower pressure.

11 **Alcohol** The studies of Alvarez and Stanley⁶ on inmates of a large state prison indicate that the more or less constant use of alcohol does not permanently affect blood pressure. If anything it causes it to be lower in the later years of life.

12 Tobacco The use of tobacco does not seem to have much permanent effect on blood pressure. Alvarez and Stanley⁶ found that nonsmokers have slightly lower pressures than smokers. According to Johnson⁴⁷ the act of smoking if it has any effect at all slightly lowers the pressure. Jewery⁴⁵ found a slight increase during smoking.

Recent extensive studies by Hines and Roth⁴¹ indicated that cigarette smoking produced elevation of the blood pressure in the majority of individuals tested by a standard smoking test. The excessive rises in blood pressure from smoking occurred only in patients who had evidence of an inherently hyperreactive vascular system as measured by the cold pressor test. The effect of tobacco smoking however is not due to a nonspecific stimulus but is the result at least in part of some element in tobacco smoke which causes vasoconstriction.

13 Weight As Alvarez and Zimmermann⁷ have pointed out it is not safe to compare mean blood pressure in any two groups of persons unless the weights of the persons are known and factors deduced from these weights are used to correct the figures expressing mean pressure. The technic for making the correction is similar to one used by statisticians in the correction of mortality rates. Unfortunately more information is needed in regard to this relationship between weights and pressure and until it is available the correction of means will be somewhat unsatisfactory. The tables that are to be found in articles by Symonds⁹² Alvarez and Zimmermann⁷ Huber⁴³ Hartman and Christ³⁴ Burlage¹³ and Alvarez and Stanley⁶ are all somewhat different.

It has never been demonstrated clearly that the higher blood pressure readings obtained in obese persons are not due mainly to the greater difficulty in compressing the brachial artery in a fat flabby arm. Against such an explanation is the fact demonstrated by Symonds⁹² Alvarez and Zimmermann⁷ and Alvarez and Stanley⁶ that fatness before the age of 35 or 40 years does not have much effect on blood pressure. It is after this that most of the effect comes.

14 Body Build It has been generally assumed that blood pressure tends to be higher in short stocky short necked persons than in tall thin rangy ones but the anthropologic and statistical study of Alvarez and Stanley⁶ did not reveal any significant correlation between blood pressure and the pyknic index. This index expresses numerically the relation between the bulk of the thorax and the length of the legs.

15 **Height and Surface Area** Alvarez and Stanley⁶ could not find in state prisoners any significant correlation between systolic blood pressure and either height or surface area

16 **Climate and Temperature** Tung⁹⁶ compared the pressures of 58 Americans before and after they had resided for two or three years in China. The average figures in America were 118 mm systolic and 76 mm diastolic; in China they were 109 and 63 mm. *Life in America and in China is so different that it is perhaps unwise to attribute all of the observed differences in blood pressure to climate alone* (see Chapter XLVIII). Foster⁹⁷ examined 34 men and women after a residence of one or more years in China. The average systolic blood pressure was from 8 to 14 mm lower in China than in America. Forty members of the faculty of the Peking Medical College showed a mean pressure 9 mm lower than it was when they were living in America.

Kilborn⁵⁴ examined 700 university students in Szechwan (latitude 30°) and found a mean systolic pressure of 111 mm and a diastolic of 70 mm. Nine Canadian and American boys raised in Szechwan with a mean age of 15 years showed a mean systolic pressure of 120 mm and a diastolic of 80 mm. The latter group is small for comparison with the Szechwanese students but so far as the data go they indicate that the difference observed is due to differences in race or amount or quality of food and not to climate. Kao⁵⁰ found that students in Hunan (latitude 34°) had systolic pressures higher than those of students in Canton (latitude 23°). Cadbury¹⁵ studied 774 Chinese students in Canton. Those between the ages of 7 and 14 years were found to have a mean systolic pressure of 83 mm and a diastolic of 51 mm; those between the ages of 15 and 20 years showed pressures of 101 and 62 mm; and those between the ages of 21 and 30 years showed pressures of 101 and 68 mm.

Brown¹¹ in an extensive study of daily and monthly variations in blood pressure found a tendency to low readings in warm weather. Alvarez and Stanley⁶ examined 74 prisoners on a warm day and 135 on a cool day. The mean systolic pressure of the first group was 118.8 \pm 1.10 mm and of the second 122.7 \pm 0.8 mm. Since different groups were used this evidence is only suggestive.

On the whole there would seem to be little doubt that blood pressure readings that are to be used for statistical purposes should always be accompanied by a record of the temperature of the environment at

the time of the study. It seems probable that the person who is perspiring freely and whose tissues are relaxed by warmth will have a lower pressure than the one who is somewhat tense from cold. It may be found some day that the big differences observed in the mean pressures of several thousand university freshmen at the same school but in different years are due in part to differences in temperature during the week in which the examinations are made (Alvarez⁶).

17 Barometric Pressure According to Franke²⁸ there is some correlation between barometric pressure and blood pressure but his published figures are not convincing. O'Sullivan⁷⁰ found that the systolic blood pressure increased where miners descended into mines.

Comment In order that a blood pressure reading may be of statistical value it should be made carefully with a good mercury manometer and a cuff of standard width. The mercury should be allowed to fall gradually and the reading should not be made carelessly to the nearest multiple of ten. If a second reading is made the cuff should first be deflated and the arm allowed a moment's rest. Readings should be made with the auscultatory method. All the subjects should be examined in the same position and the same arm (right or left) should be used. Note should be made on the length of time that the subject waited before examination, also whether he hurried to the appointment or while waiting stood partly dressed in a cold room, took a warm bath or did anything out of the ordinary.

The temperature of the environment should be noted and also the time of day and day of week. If more than one reading is made at short intervals all of the subjects must be treated in the same way and only one method must be followed in reporting the results. It is not good statistical practice to use the first record made on ten men and then to juggle with the eleventh man until his measurement is brought down or up to the desired or expected point. It will be necessary of course to include data in regard to sex, age and weight. In any published report of blood pressures it should be stated whether weight was taken with or without clothes.

The presence of a fast pulse should be noted as this can probably account for an increase in blood pressure. Note should be made also of the presence of a cold or other transient infection or of fatigue from a hard night out. Finally in every paper on blood pressure all the data

should be presented in the form of a distribution table so that they can be used again and analyzed further by subsequent students of the subject

COLD PRESSOR TEST

A simple test for this response first described by Hines and Brown³⁹ consists of immersing the patient's hand in ice water and determining the vasomotor effect as shown by changes in the blood pressure. It was found that 99 per cent of patients responded by a rise in pressure and that this response was remarkably constant over a period of time. In a later report these authors⁴⁰ report data accumulated from the study of 571 patients so tested. The following technique was observed:

The patient is allowed to rest in a supine position for 20 to 60 minutes in a quiet room. The basal level of pressure is approximated from several readings; the cuff of the sphygmomanometer is adjusted on one arm of the patient and the opposite hand and wrist is immersed in ice water. The reading at the end of 30 and 60 seconds is ascertained, the hand removed from the ice water and readings are taken every two minutes until the level is again reached. The maximum response or ceiling which is frequently obtained in 30 seconds and held for a variable period of time and the amount of increase or range are the two important values obtained in this way.

These reactions seem to be constant over long periods of time and are characteristic for the three groups—normal, normal hyperreactives and hypertensives—into which the authors have divided their subjects.

1. **Normal (Normal Blood Pressure)** The mean increase was 11.1 mm systolic and 10.6 mm diastolic with a range of 0 to 22 mm.

2. **Normal Hyperreactive (Blood Pressure Within Normal Limits)** Mean increase was 29.4 mm systolic and 24.5 mm diastolic. This group in the opinion of Hines and Brown is most important from a prognostic standpoint. It is not a definitely established fact that this reaction is a precursor of hypertension, but there is a very strong probability that it will be so proved. Seventy-eight of the 90 patients in this group gave a positive hypertensive family history, while only 14 per cent of the first group had positive histories. Three of the patients examined in 1932 had developed essential hypertension by 1936.

3 Essential Hypertension The mean rise was 47.2 mm systolic and 34.3 mm diastolic in the organic group and 34.4 mm and 25.4 mm in the preorganic. All these patients had high ceiling values.

NORMAL BLOOD PRESSURE

The term normal blood pressure must of course always refer to the ideal or commonest pressure found in persons of average weight and of a certain age. Obviously it is difficult to get measurements on large groups of unselected or presumably normal persons. The ideal way would be perhaps to put up booths in various parts of several towns and cities and there to make a pressure reading on each of the first 5000 persons to pass by. Since this can hardly be done the next best plan is to examine students, soldiers, employees of large institutions, state prisoners and inmates of old people's homes. Office patients are not suitable because they constitute a selected group. Similarly soldiers and aviators are not entirely satisfactory because they have already been selected for their special fitness and freedom from defects. Applicants for insurance are not always satisfactory because so many apply the minute they have reason to believe they are ill. Furthermore as has already been pointed out in their case the examiner so commonly works under duress.

1 *Discordance in Results Reported by Different Observers* In a review of the reports of the various investigators one of the great difficulties encountered arises from the fact that one physician will measure pressures in children, another in high school students, another in college students, another in soldiers or prisoners or insurance risks of middle age and another in aged inmates of almshouses or old people's homes. Each one plots a part of the desired curves expressing the relation in males and females between blood pressure and age but unfortunately when these parts are brought together onto one sheet of coordinate paper their ends rarely meet and many puzzles remain for solution.

As Alvarez^{3, 4} has shown even when one set of examiners works fairly carefully in a university infirmary from year to year decided variations will be found in the mean pressure of the thousands of freshmen examined. These variations are far too large to be accidental and they have been observed in more than one institution. They have been noticed also by insurance examiners (Symonds⁹²). It would seem that some of the differences must be due to personal factors others may well be due to

certain cycles of human metabolism which are just beginning to be recognized (Moore and Cooper,⁷⁰ Griffith and his associates,³¹ and Brown¹¹); others again may be due to the fact that some examinations were made predominantly in the morning and others predominantly in the afternoon. In this connection, what is probably a most illuminating observation was made by Diehl and Lees²¹ as they studied 100 male university students. The mean pressure in the morning was 115.0 ± 0.3 mm. and in the afternoon 124.1 ± 0.3 mm. Such a difference alone would be enough to explain all the variations which have been found in standards of normal offered by different investigators such as in almost identical groups as studied by Jackson¹⁴ and Diehl and Sutherland,²² granting that some did most of their examining in the morning and others in the afternoon.

2. **Desirability of Using the Mode and Not the Mean:** It is unfortunate that almost every attempt made so far to set up standards of normal blood pressure has been more or less invalidated by the fact that the average or the index of central tendency used has been the arithmetic mean and not the mode. The man who is not statistically trained will always use the one average with which he is acquainted and this, unfortunately, is the arithmetic mean. As everyone knows, this is obtained by adding the measurements and dividing by their number. This one out of several possible averages suffers from the serious defect that it is influenced, sometimes markedly, by data secured from abnormal persons. Actually, if there are enough abnormal persons in a group, the arithmetic mean will have practically no value, because it will represent a compromise between the normal and the abnormal figures.

To give an example: An anthropologist may be studying the stature of a group of persons living on a small island in the Pacific. The laborers on this island probably are Japanese and the overseers and the men in the business office are Americans. If the anthropologist were to put down at the bottom of a sheet of paper a row of figures representing stature in inches and above each figure a dot for each man of that particular height, he would find when he had finished that the dots had made two mounds, one with a peak or mode perhaps at about five feet four inches and another with a peak at about five feet nine inches. Another anthropologist seeing this chart would know immediately that his colleague had been dealing with a composite, heterogeneous population: One made

up of a large group of persons of low stature together with a small group with high stature. The mean or average stature of such a composite group would be expressed by a figure devoid of value or interest because it would fail to tell anything about the stature of either Japanese or Americans. The arithmetic mean fails also to warn the investigator that he is dealing with a composite group.

It is greatly to be hoped therefore that in all future work on blood pressure little attention will be paid to arithmetic means but that instead modes for the different ages will be published. It is really this mode that the physician wants to locate when he is searching for criteria of normal. He does not want a compromise figure; he wants to know the commonest or most usual pressure in supposedly normal persons and this obviously is to be found on the scale below the principal peak in the distribution polygon. Another valuable bit of information that the distribution polygon supplies is the range of normal values.

3 Influence of Age Systolic pressure in newborn infants of both sexes has been found to be between 43 and 55 mm (Reis and Chaloupka⁷⁷ Rucker and Connell⁷⁸). It tends to rise rapidly so that at the end of the first week it is about 60 mm and by the end of the first month 82 mm (Seitz and Becker⁸⁴). Judson and Nicholson⁴⁸ who studied 1244 normal children found a systolic blood pressure of approximately 91 mm in the group aged from three to nine years. The pressure was about 99 mm in children aged from 10 to 12 years and it was approximately 104 mm in the years from 13 to 14.

The diastolic pressure did not show much change with the increasing age. Erber and James²⁵ studied 1101 boys and girls with ages ranging from 3 to 17 years. In both sexes systolic pressure increased from about 89 mm at the age of four years to 115 mm at the age of 16 years. The diastolic pressure ranged from 60 to 75 mm.

Stocks and Karn⁸¹ made a careful analysis of blood pressure in 1163 normal persons aged from 5 to 21 years inclusive. Unfortunately most of the age groups were too small for adequate statistical treatment. Their figures for mean systolic pressure showed a steady increase from 85 mm at the age of five years to 130 mm at the age of 17 years. After this there was no increase.

Burlage^{1*} who studied 1700 girls from school and college found a rapid increase in systolic blood pressure from 104 mm at nine years to

approximately 124 mm at 14 years. The pressure remained about 124 mm during the fifteenth year and then there was a rapid fall of about 10 mm to the age of 18. After this until the age of 26 years, the pressure remained fairly constant at a level of about 110 mm. The diastolic pressure rose evenly from 63 mm at the age of nine years to about 76 mm at the age of 14 years and after this remained constant.

Alvarez⁴ studied 365 boys and 288 girls in high school. There were three groups corresponding to ages of 13, 14 and 15 years. During this short period of life the mean systolic pressure of the boys rose from 110 to 121 mm while that of the girls fell from 121 to 120. The range of the measurements was much wider in boys than in girls and there was much more hypertension found among them than among the girls. In fact this defect was found commonly among the boys, some of whom were normal enough to be taking a successful part in athletics. The crude mode of the boys' pressure ranged during the three years from about 112 to 122 mm while that of the girls remained constant at about 122 mm. The measurements were made with the auscultatory method and with the subjects sitting.

Kilborn⁵⁵ has emphasized the variability of blood pressure in young persons. He studied 51 students at four different times: (1) About the close of the academic year when examinations were due; (2) in September at the close of summer vacation; (3) just before the Christmas examinations; and (4) in the spring about the time when there happened to be some violent agitation among the students. He found the blood pressures greatest at the fourth determination and lowest at the second. Tigerstedt⁹⁰ found similar rises in blood pressure before examinations.

Probably the most extensive studies made on college students have been reported by Alvarez^{3, 4}. In his second paper he analyzed the pressures of 6000 men and 8934 women. Among the men the mean systolic pressure rose from 129.5 mm at the age of 16 to 130 mm at the ages of 17 and 18 years. After this the pressure dropped gradually to 127 mm at the age of 30 years. The mean for the women was about 118 mm at the ages of 16 and 17 years. After this it dropped steadily to the age of 24 and after the age 26 it rose steadily to 119 mm at the age of 30. The modal or most typical systolic pressure for the men fell from 127 mm at the age of 16 to 118 mm at the age of 28; after this it rose. The

modal pressure for the women dropped rapidly from 118 mm at the age of 16 to 111 mm at the age of 24 after this it rose to 116 mm at the age of 40

This tendency for the blood pressure to show a slight drop between the ages of 17 and 25 may seem surprising to many physicians but its existence has been definitely confirmed by several investigators and actually when the data published by insurance examiners (Symonds²²) are studied more carefully it will be found that they show a somewhat similar absence of a rise until after the age of 40 years In a series of 42 133 accepted risks of normal weight the mean systolic pressure remained between 123 and 124 mm until the age of 39 years

Alvarez^{3 4} was surprised to find so many boys and college students with high pressure and at first rather doubted the accuracy of his measurements but his observations have since been confirmed by several investigators working in different colleges It now seems probable that there is an unusual degree of lability of blood pressure among boys and youths about the ages of 17 and 18 years *This may perhaps be due to a greater sensitiveness of sympathetic nerves or to a greater responsiveness to emotion, and to such excitement as is occasioned by a physical examination* Twenty two per cent of the male freshmen and two per cent of the female freshmen at the University of California were found to have a systolic pressure exceeding 140 mm As was shown by Diehl and Sutherland²² many of the high pressures are not constant and do not represent true hypertension They doubtless have some significance in regard to the later health of the individual but only time will tell what it is

Diehl and Sutherland²² who worked with students at the University of Minnesota found as Alvarez did that many show a high pressure at the first examination In 1922 with 1686 male freshmen the mean systolic pressure was 126.9 ± 0.2 mm In the years 1923 and 1924 blood pressure was taken during the examination of 4316 more students This time all those with a pressure higher than 140 mm were held for several more readings These later readings were usually lower than the first and when they were averaged with the data secured from students who had normal pressures to begin with a mean of 122.7 ± 0.1 mm was obtained

Barach and Mark⁸ studied 656 young men between the ages of 19 and 25 years. They found 90 per cent with systolic pressures less than 150 mm. and 87 per cent with diastolic pressures less than 100 mm.

Lee⁶⁰ studied 662 freshmen and found a mean systolic pressure of 120 mm. and a diastolic of 80 mm. Woley¹⁰⁰ studied 1000 healthy persons between the ages of 15 and 65 years. The palpatory method was used. The mean systolic blood pressure of the men was 127.5 mm. and of the women 120 mm.

Addis¹ studied soldiers for basal and active pressures. To get the basal pressure, the soldier was awakened in the morning by the application of the cuff to the arm. The mean pressure obtained in this way in the case of 66 normal men was systolic, 99 mm., and diastolic, 71 mm. After the men had been up and about, the corresponding figures were 127 and 78 mm.

Alvarez and Stanley⁹ studied blood pressures in 6000 state prisoners. They found that modal blood pressures remained almost constant, about 115 mm. from youth to old age. This is perhaps a little lower than the corresponding figure for men out in the world, but it must be remembered that prisoners are not fatigued or worried by the struggle involved in making a living; to a certain extent, then, their pressures are basal. The mean pressure was fairly constant, about 117 mm., until the age of 40 years; after this it rose. The evidence indicates that most of the men who had hypertension at the age of 40 years had it at the age of 20 years, and that a pressure of 115 mm. is just as normal, and a pressure of 145 is just as abnormal, in an old man as in a young man. The modal diastolic blood pressure was 68.5 mm. in the younger men and 73 mm. in the older men.

Saller⁷⁰ studied the blood pressures of 7382 men and 5197 women between the ages of 21 and 89 years. He found that the range of systolic blood pressure for normal men remained between 98 and 144 mm. during the ages between 21 and 47 years, inclusive. The range for normal women between the ages of 21 and 35 years was from 99 to 138 mm.; between the ages of 35 and 47 years it was from 100 to 155 mm. His study indicated an increase in the normal blood pressure following the menopause of women and following the age of 50 years of men. Lewis⁶¹ found a highly significant positive relation to age in the systolic, mean and pulse pressures but not in the diastolic pressure. His studies indicated that

the systolic, mean, and pulse pressures increased gradually from 40 to 62 years and rapidly from 62 to 85 years. After 90 years, the pressures seem to decline.

4. *Range of Normal:* The distribution curves published by Alvarez and Stanley⁶ show that the lower limit of normal pressures must be about 90 mm, whereas the upper limit is about 140 mm. These figures are in agreement with the impressions which have been gained by insurance examiners. Many physicians become alarmed when they find a systolic pressure between 90 and 100 mm, but insurance statistics show that men and women with such pressures usually have long lives. Indeed, Robinson and Brucer¹⁰² have concluded that the normal range of systolic blood pressure is between 90 and 120 mm of mercury and that the normal range of diastolic blood pressure is between 60 and 80 mm. Hines¹⁰² study indicates that patients whose blood pressures when first determined in the clinic are less than 120/70 almost never develop hypertension, while patients whose diastolic pressures under the same circumstances exceed 85 mm of mercury are almost certain to develop frank hypertension subsequently.

5. *Sex:* It seems obvious that sex is one of the most important modifying factors in blood pressure. First, it should be noted that before puberty there is no sexual difference in systolic pressure. With the development of the gonads, the pressure of boys increases rapidly, so that by the age of 18 years their mean and modal pressures are about 10 mm higher than those of girls. Figures supplied by Alvarez⁷ show that after the fall in the mean and modal pressure which takes place after the age of 18 years, there is a rise which appears first in women, and which is also more abrupt than in men. As a result, some groups of data^{7, 79} show that at the age of 40 years the line representing the mean pressure in women crosses the corresponding line for men.

A number of investigators have found that in the later years of life women tend to have higher pressures than men. It is interesting to note that the two striking divergencies in mean pressure in the two sexes take place at puberty and about the time of the menopause. Alvarez and Zimmermann⁷ have shown also that pressures tend to be higher in women who, fairly early in life, show signs of defective pelvic organs. Alvarez believes that a tendency to hypertension, which is probably inherited by both sexes,

can, for many years, be submerged in the women of a family if their ovaries function normally

Conclusions: 1 Satisfactory standards of normal blood pressure are not yet available, due largely to the fact that the many investigators have not used standard methods of procedure, and have failed to publish distribution tables and to designate the mode which is the desired measure

2 *The old rule that normal systolic blood pressure is equivalent to 100 plus the age of the person being studied is certainly not true, because among normal persons there is no steady increase of blood pressure with age*

3 The normal systolic pressure for men aged between 20 and 40 years is about 120 mm, and for women of the same ages about 113 mm. The normal range for both men and women is roughly between 90 and 140 mm. Normal diastolic pressure for women is about 70 mm, and for men about 75 mm

It is significant that many old men and women have systolic blood pressures of about 120 mm. It is probable that a basal systolic blood pressure of 150 mm is as significant of abnormality at the age of 50 as it is at 20

4 It is important to know that blood pressure may be influenced in a physiologic way by emotion, time of day, day of week, season of the year, temperature, climate, exertion, sleep, meals, posture, position of the arm, rest, and probably by other, as yet unknown, factors. *Rest in bed will frequently lower the blood pressure by from 50 to 80 mm, and physicians must be careful not to ascribe to the use of drugs a lowering of blood pressure which is purely physiologic in origin*

5 The only way in which a physician can learn much about the blood pressure of an individual is to make readings at hourly intervals for two days or more. Then something will be known about the range of normal variations and about the influence of rest, sleep, and work

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CHAPTER XLIV

CAPILLARY CIRCULATION

By ARTHUR C. DEGRAFF, M.D., and CHARLES E. KOSSMANN, M.D.

Clinical Importance: In a discussion of the various components of the circulatory apparatus, the major emphasis is usually placed on the heart. From a mechanical viewpoint this is probably correct, for it is upon the efficiency of the heart as a pump that the maintenance of an adequate flow through the circulatory system depends. However, when the circulatory system is considered as a method of supplying the cells of the body with the necessary substances to sustain life as well as to remove waste products, the capillaries become exceedingly important. It is at the capillary endothelium and nowhere else in the entire circulatory system that exchange of substances can occur between the blood and the intercellular lymph. The capillary endothelium, the total surface of which is estimated to be 6300 sq. m.,³⁰ permits the passage of water, oxygen, carbon dioxide, electrolytes, occasionally certain colloids, and even blood cells. The importance of the capillary circulation is, therefore, quite evident; but, because of the difficulties in studying the capillaries, particularly their intimate physiology, exact knowledge is quite fragmentary.

ANATOMY AND PHYSIOLOGY

Although the arteries down to the smallest arterioles have a definite muscular coat which envelops the entire vessel, the capillary wall consists chiefly of a single layer of thin polygonal endothelial cells. Arranged at intervals on the outer side of the endothelium are branching cells which have been demonstrated by Vimtrup⁵⁸ to be muscle cells. Since these cells were originally described by Rouget⁵¹ in 1873, Vimtrup has named them after the discoverer and today they are universally known as Rouget cells. According to Krogh³⁰ it is by means of these muscle cells that the capillaries are able to alter their caliber regardless of their contents.

Recent studies throw serious doubt upon this concept. Sandison⁵² and Clark and Clark^{13, 15} using the rabbit's ear and a transparent cham-

ber technic, were unable to see spontaneous capillary contractions. Micro-manipulation experiments on tissues of the frog and mouse reported by Zweifach,⁶³ and by Zweifach and Kossmann⁶⁴ indicate that capillaries are

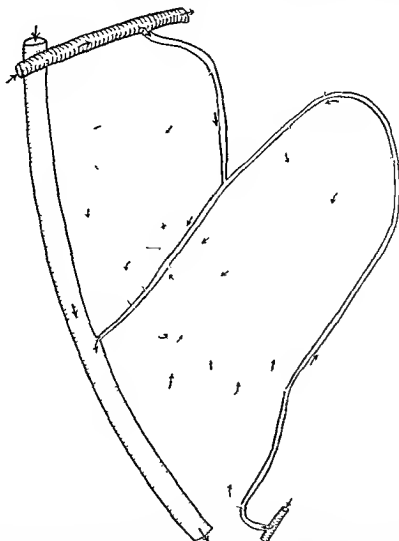


FIGURE 1 Camera lucida outline of vascular pattern of small blood vessels in the frog. Arterioles are striated, venules are stippled, muscular capillaries (A-V bridges) have solid outlines, and non-muscular (true) capillaries have broken outlines. (After Zweifach.)

of two types: (1) 'Muscular capillaries,' which possess pericapillary cells capable of causing only a partial constriction of the capillary lumen when prodded with a microneedle, and (2) "nonmuscular" or "true capillaries," which possess no pericapillary, contractile cells. In neither

type could a contractile response be elicited by stimulating the endothelial cells comprising the walls

In the resting state the true capillaries contain no blood. The muscular capillaries on the other hand form a pathway of continuous flow from the arterial to the venous side of the circulation (Fig. 1). They appear to carry on the basal work of the capillary bed. The true capillaries become active only when local tissue metabolism demands it. It is true that the latter show a gradual decrease in calibre when inactive but direct observation in animals fails to show rapid contractions such as are exhibited by arterioles in response to a mechanical stimulus.

The total capacity of the capillary system is tremendous and it has been estimated that if all the capillaries were open to their greatest diameter all the circulating blood could easily be contained within them.

A consideration of the factors regulating the size of capillaries and the rate and amount of flow through them cannot be undertaken without keeping in mind the existing differences of opinion regarding capillary contractility. Conceivably three mechanisms may be involved.

1 **Nervous Regulation Central and Local.** Anatomical studies have failed to establish a central nervous system control over capillaries. Physiological evidence is questionable since it is difficult to separate arteriolar activity from capillary activity, the one depending largely upon the other. Proof that a local sensory nerve axon reflex exists such as Lewis³⁷ has demonstrated in the case of arterioles of the skin is at present lacking.

2 **Local Regulation by Substances Formed in the Tissues.** When ever the skin is stimulated strongly by such agents as stroking, heat, cold, ultraviolet light, strong acids, alkalis or electrical currents, the reaction is a dilatation of the capillaries. Almost simultaneously a dilatation of the supplying arterioles also occurs. A wheal is formed due to increased permeability of the capillaries just beneath the site of injury. Experimentally⁶³ irritation of a large amount of pericapillary tissue with a microneedle often causes dilatation of the corresponding arteriole first to be followed in a few seconds by dilatation of the capillaries. This fact seems to establish the reflex nature of this type of arteriolar dilatation. It is believed⁶³ that the capillary dilatation accompanying it is due to two factors. A reduction in what may be called the turgor of the individual endothelial cells plus the increased capillary blood flow and

capillary blood pressure that goes with increased arteriolar supply. Lewis gives abundant evidence to show that in the tissues immediately affected by the stimulus a metabolite is formed whose action is physiologically identical with that of histamine. This chemical called H substance by Lewis³⁷ causes local dilatation of the capillaries dilates the arterioles reflexly through an axon reflex and produces tissue edema due to increased permeability of the capillary wall. The constant formation of small amounts of the H substance is said³⁷ to regulate the blood supply to the tissues.

3 Hormone Regulation. Pituitrin has been found by Krogh³⁰ to cause a constriction of the capillaries. He presents evidence favoring the view that pituitrin is responsible for the tonus of the capillaries. It conceivably balances the dilating effect of the tissue metabolites. Lewis³⁷ however believes that in the concentration to be found in the circulating blood pituitrin has little if any effect on the caliber of the capillaries. The problem is still unsettled.

The action of epinephrine on the capillaries is also debated. The great question appears to be at what concentration epinephrine ceases to have a constricting effect and begins to cause a dilatation. If true capillaries have no inherent ability to contract the role of epinephrine in regulating them becomes obscure.

A review of the means by which capillary size and caliber are controlled therefore reveals that substances liberated locally are probably most important. These bring about an increase in capillary caliber by direct action on the endothelium and through a local reflex cause dilatation of the corresponding arterioles. This results in local hyperemia. The role of the central nervous system and of hormones in the light of available evidence is uncertain but appears to be a secondary one affecting capillary activity by changing arteriolar activity.

The arteriovenous anastomoses studied and described by Sucquet²¹ by Hoyer²⁷ and more recently by Missou⁴⁰ are probably of considerable importance in determining how much blood gets to a capillary bed under varying conditions. What is known of these vessels has been summarized by Clark.¹² In man they are numerous in the nailbeds and distal pads of the fingers and toes, in the penis and in the glomus coecygeum.^{12 14 22 23 27 40 48} they are rarely found in the heart⁵⁹ in the pericardium⁴⁴ and in the pramater⁵⁷. That they exist elsewhere

in human tissues is probable though not proven. From the experiments of Grant and Bland²³ it appears that these shunts are important in regulating the skin temperature of the fingers.

Substances may pass through the capillary endothelium by three methods—diffusion, filtration and permeation. The capillary wall forms a semipermeable membrane and within certain limits behaves according to the physical laws of diffusion.³⁰ For crystalloids and gases the rate of diffusion is proportional to the differences in pressure on each side of the membrane and the diffusion constant of the substance passing



FIGURE 2 Photograph of capillaries of nail fold
(Strauss and DeCraff. *Am Heart J*)

through. The colloids of the blood are held back, however, and are responsible for the oncotic pressure exerted by the blood in the capillaries, this pressure being of the nature of 30 mm. of mercury.⁵⁰ Opposed to this is the capillary blood pressure which is also approximately 30 mm. of mercury. Changes in balance between these two pressures largely control the filtration of capillary fluid. Capillary permeability may be increased, usually by injury, to a point where plasma protein and even cellular elements escape into the tissues. The ordinary process of inflammation is an example.

METHODS OF CLINICAL STUDY

Visualization. The study of the capillaries in man presents certain difficulties. Chief among these is the inaccessibility of these vessels, except in the skin. The entire capillary loop is best observed in the nail folds of the fingers or toes. The capillaries in the papillae of the fold lie more or less horizontally, while elsewhere they are arranged more vertically.

The capillaries may be visualized directly⁶ or by instantaneous photomicrography^{6, 53} or by cinematographic microscopy¹⁰. The difficulties in all methods arise from the glare reflexes and haziness that go with it. These can be surmounted in large part with the Ultropak of Heine²⁵. With this method indirect illumination the rays of which are outside the rays of the observation optic is used. It is sufficiently practical for clinical use¹⁹.

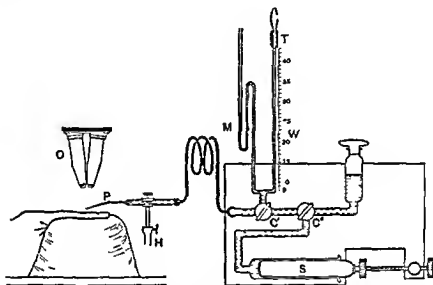


FIGURE 3 Diagram of apparatus for determination of capillary pressure by microinjection (F. M. Lands & Heart)

It is perhaps important to point out that by no method at present available can the capillary endothelium be seen through the intact skin of man. The image observed in the capillary microscope is the corpuscular stream. Clinically its size, variations in size, tortuosity, and rate of flow^{4, 12} are noted. With photographic methods the area of capillary blood or the number of capillaries per unit of skin can be measured^{9, 11, 13} (Table I).

Capillary Pressure. Many methods have been described for determining capillary pressure. These fall into two general classes: The direct and the indirect. In the first class probably the most accurate is the *direct method* devised by Lands¹³ (Fig. 3). A micropipette with an orifice of 8 to 12 microns in diameter is inserted in the capillary. It is controlled by a Chambers¹¹ micromanipulator which is capable of moving it vertically as well as horizontally. The pipette is filled with

fluid from a reservoir and connected to a manometer. Pressure is applied until only a few corpuscles remain oscillating at the tip of the pipette. A reading is then taken.

This method unfortunately is not readily adaptable to clinical use. It requires an extremely high degree of skill on the part of the operator and an even higher degree of patience on the part of the subject. Special training is necessary to operate the micromanipulator successfully. To apply it to microinjection of human capillaries is a task for the expert. Then too, before insertion of the pipette into a capillary, it is always necessary to remove a thin layer of epidermis with a keen razor blade. Even with this precaution, the author states, breakage occurs frequently. Landis apparatus, however, obviates many technical errors of the method of Carrier and Rehberg¹⁰ so that the results obtained may be taken as the standard measurement of capillary pressure in man. The normals obtained by the method: average 32 mm. of mercury in the arterial limb, 20 mm. of mercury in the loop, and 12 mm. of mercury in the venous limb.

The available *indirect methods* for measuring capillary pressure have been reviewed by Stray and DeGraff⁵⁴. These may be subdivided into those which use blanching of the skin as an endpoint, and those which use as the endpoint some phase of cessation of flow as visualized microscopically. The results obtained when skin blanching is used as an index of capillary pressure are fallacious for the following reasons: (1) Intimal blanching of the skin is due chiefly to an evacuation of the superficial venous plexuses. (2) Variations in skin pigmentation of different subjects make the endpoint difficult to determine. (3) personal equation is too important so that different workers using the same apparatus obtain widely varying results. (4) several of the devices in use have inherent defects which make for inaccurate determinations.

It seems that an indirect method with a more definite endpoint is the one of choice for routine clinical use provided that it is accurate and practical to make, maintain and use. The methods which permit of direct visualization of capillaries are those of Lombard³⁰, Guilbume²⁴, Rajka⁵⁰, Krauss⁻⁹, Danzer and Hooker¹⁸, Kylin³¹ and Stray and DeGraff⁵⁴. With the first three and the last, pressure is applied to the skin surface by a rigid transparent material; with the others it is applied by an elastic capsule. Even using the endpoint of slowing of

capillary flow however the pressures obtained in normals by these various methods vary from 1 mm to 45 mm of mercury Here too different workers using the same device have obtained different results

These facts without question seriously diminish the importance of clinical capillary blood pressure determinations by any but the direct method but they do not make previous observations useless The same investigator using the same method in normal and abnormal subjects may obtain clinically important relative differences in the two even though the absolute values are inaccurate

The method of STRAY and DeGraff³⁴ is simple to use and quite accurate although the use of initial slowing of blood flow through medium sized capillaries as an endpoint has been criticized³⁴

TECHNIC OF STRAY AND DEGRAFF METHOD The apparatus consists of a lever (Fig 4A [a]) a spring (d) a finger rest (e) and a scale (c) The lever is approximately 20 cm long At one end it contains a circular plate of glass (b) to which is attached a smaller plate of glass (f) 2 mm in diameter Between the glass and the fulcrum a screw is inserted into the lever which has attached to it a spring (d) the other end of which is attached to the base of the instrument On the lever rests a movable rider (g) used in calibration of the instrument The pointer of the lever is in proximity to a scale A rest (e) is provided for the finger which can be raised or lowered at ease in a vertical plane to bring the latter into proper relationship to the glass (f) The lever can be kept level by adjusting the screw which regulates the tension of the spring

The instrument can be placed conveniently on the stage of a microscope and clamped there to prevent movement Reflected light is used The stronger the light concentrated at the point of examination the clearer the view of the capillaries obtained Good results however can be obtained by placing an ordinary microscope lamp on the base of the instrument which is on the stage of the microscope so that the light is concentrated on the finger A magnification of about 90 to 100 \times is used

To calibrate the instrument at any time the weight is placed on the rider the amount of deflection caused is noted and by simple arithmetic a factor is found which when multiplied by the deflection obtained in measuring capillary pressure gives the pressure directly in millimeters of mercury The instrument which is pictured herewith is calibrated so that each millimeter on the scale equals two millimeters of mercury pressure

A reading is taken as follows The patient is at rest in the sitting posture with his hand well supported at heart level to obviate differences due to hydrostatic pressure A drop of cedarwood oil is placed on the finger at the nail fold The finger is placed on the rest (e) and raised by means of the

screw so that the glass (*f*) comes in contact with the skin at the nail fold. By watching the movement of the lever on the scale the point of contact is easily determined. The microscope is then focused on the capillary bed

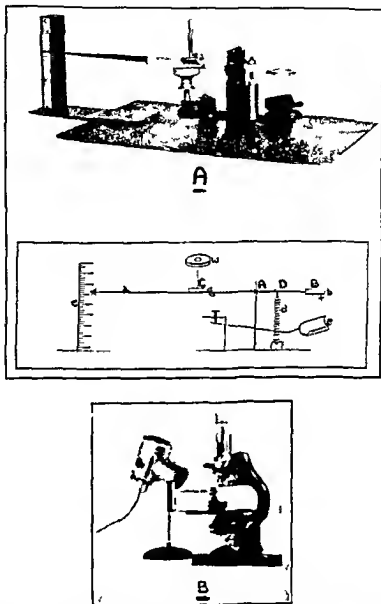


FIGURE 4. Indirect method of Strax and DeGraff. *A*: A close up photograph of the apparatus below is a sketch showing the principles of construction of the instrument. *B*: Apparatus set up with microscope and lamp (Strax and DeGraff, *Am. Heart J.*)

through the glass (*b*). Pressure is easily applied by means of the screw raising the finger rest against the lever. The other hand manipulates the focus of the microscope. When the endpoint is reached the pressure applied is

read off directly on the scale in millimeters of mercury. One person can easily make a reading.

Readings are taken on two or three capillaries in the same finger and the results averaged. Only the more superficial capillaries are used.

In a series of 50 normal subjects the readings obtained by this method in 70 per cent were 22 to 25 mm. of mercury, in 20 per cent were 18 to 21 mm. of mercury, and in ten per cent were 26 to 29 mm. of mercury.

Capillary Fragility. There are three methods available which are said to measure capillary fragility.

1. **Rumpel-Leede Test.** Rumpel's original experiment of producing hemorrhage in the skin of the antecubital fossa in cases of scarlet fever with the use of a Bier compression band was developed into a clinical test in 1911 by his assistant, Leede.²⁰ Various modifications have been used by many observers, especially as an aid in the recognition of less severe forms of scurvy. Recently the test has been quantitated by Gothlin²¹ as follows: The patient is recumbent and the arm horizontal. A circle 6 cm. in diameter is marked out with ink on the anterior surface of the elbow. Because high pressures influence the arterial affluents of the extremity, Gothlin recommends that infradiastolic pressures be applied with a blood pressure cuff above the elbow. Pressures of 35, 50, and 65 mm. of mercury are used, beginning with 50 mm. of mercury. After 15 minutes the pressure is quickly released and the petechiae in the circular area counted with the aid of a hand lens. If no petechiae appear the test is repeated on the same arm using a pressure of 65 mm. of mercury. If the pressure of 50 mm. of mercury produces one to four petechiae, no further trial is necessary. The limit of the capillary strength is then somewhere in the neighborhood of 50 mm. of mercury. If there are more than four, then the other arm should be tested with a pressure of 35 mm. of mercury. If at least two petechiae are plainly visible at this pressure, too, the limit of capillary strength is then less than 35 mm. of mercury. If petechiae appear in one arm it should not be used for retesting during the next fortnight.

On the basis of the results cases are graded as follows:

- Grade I. Petechiae do not appear at or below 65 mm. of mercury.
- Grade II. Not more than six petechiae at 50 mm. of mercury.
- Grade III. More than six petechiae at 50 mm. of mercury. None at 35 mm. of mercury.
- Grade IV. Petechiae (at least two) at 35 mm. of mercury.

Gothlin feels that Grade III represents undoubted reduction of capillary strength, Grade IV a more pronounced reduction.

2. **Suction or Negative Pressure Test.** A vacuum is created in a small glass capsule applied to the skin.¹ The smallest negative pressure applied for one minute which causes microscopic petechiae is regarded as the endpoint.

3 Intradermal Venom Reaction⁴⁶ One tenth to 0.2 cc. (1 or 2 hemorrhagic units) of a standardized moccasin snake venom¹⁶ is injected intradermally. As a control 0.1 to 0.2 cc. of normal saline is similarly injected. A reading is made at the end of 30 to 60 minutes. The test is positive if an eddy miosis is present at the site of injection of the venom. Delayed positive reactions occur in 12 to 24 hours.

There are numerous objections to the so-called capillary fragility tests. The fact that they are positive in the majority of hemorrhagic diatheses and purpuric states not only impairs their clinical value but also emphasizes the importance of factors other than decreased resistance of the capillary wall in bringing about a positive result. The suction test yields results which differ widely in normal subjects and in different skin regions of the same individual.¹ All of the tests have been used for the determination of subclinical scurvy,^{5, 20, 47} but there is considerable difference of opinion regarding their value. The originators of the snake venom test⁴⁶ consider it of most value in classifying and prognosticating cases of thrombocytopenic purpura hemorrhagica.

Capillary Permeability Clinically capillary permeability can be estimated from the blister time.⁴⁷

An ordinary cantharides plaster is applied to the inner surface of the forearm. The time when the first elevation appears is the blister time. The protein content of the blister fluid and of blood from the ear lobe is then determined simultaneously by Petersen and Willis⁴⁷ who have worked out the following indices on normal subjects:

$$\text{Permeability Ratio} = \frac{\text{Percentage of Blister Protein}}{\text{Percentage of Serum Protein}} = 63 \text{ (range 57 to 64)}$$

$$\text{Inflammatory Index} = \frac{\text{Permeability Ratio}}{\text{Blister Time}} = 10.5 \text{ (range 3.8 to 18.9)}$$

The first is regarded as a measure of the response of the capillary endothelium to a direct stimulus and the second as a measure of the relative inflammatory response of the individual.

The test does not appear to have been used very widely.

CAPILLARIES IN DISEASE

Available observations on the capillaries in health and disease have been putrally summarized in Table I. In *shock (ex terna)* following trauma or surgical manipulation there is generalized dilatation but more particularly in the splanchnic area. Capillary permeability is greatly increased by the shock producing agent with consequent loss of fluid into

the tissues hemoconcentration and low blood pressure. Microscopically the capillaries appear engorged with static blood.⁴¹ The formation of histamine-like substance at the site of injury in all probability is the cause of the general capillary dilatation.

In *polycythemia*⁸ more capillaries are visible; the venous limbs are markedly dilated and the blood flow is considerably diminished. In *anemia* fewer capillaries are open and the blood flow is rapid.⁶²

With *hypertension*—^{3, 61} there is frequently though not always an increased tortuosity of the capillaries in the nail fold. The capillary pressure may be low or high. On this basis—³ cases of hypertension have been classified into two groups which cannot be differentiated by ordinary clinical methods. In general the capillary pressure is more directly related to diastolic than to systolic blood pressure. Wright and Duryee⁶ have shown that the rate of flow is increased in hypertension so that when using their two minute flow test it is rare to find stoppage for longer than four seconds.

In *hypotension* the capillary loops tend to be long straight and dilated. Stoppage is frequent.⁶²

During the acute stages of *glomerulonephritis* there is a fairly consistent elevation of capillary pressure.^{3, 43} This may precede albuminuria as was observed by Kohn in cases of scarlet fever complicated by nephritis. With convalescence the capillary pressure again tends to reach normal levels.

In *chronic nephritis* tortuosity of capillaries is the most constant finding more marked when hypertension has been present for some time.

From the work of Mufson⁴ it appears that high capillary pressure in the course of one of the *toxemias of pregnancy* is of poor prognostic significance both for mother and fetus.

In *congestive heart failure* with regular sinus rhythm or auricular fibrillation more capillaries per unit of skin are visible. Both the arterial and venous limbs are wider than normal and the rate of flow is decreased.¹⁶ It is probable that the edema of congestive heart failure is principally on the basis of abnormal capillary permeability secondary to increased venous pressure and injury of the endothelium.

In *Raynaud's disease* Landis¹¹ using his direct method found a drop in pressure in the capillary loop during the initial phase of an attack, a marked rise during the phase of hyperemia followed by a gradual fall

to normal pressure. The initial fall is in the hand at least due to digital artery spasm.³⁸ At first there is pallor of the digit but as available oxyhemoglobin in the stagnant capillary and venous blood is reduced cyanosis ensues.

Brown, Allen and Mahorner³⁹ found two types of capillary changes in cases of *thromboangitis obliterans*. In the first the capillaries were moderately dilated and a large number were open and active. Dependency of the limb increased this number. Flow was slow and intermittent. In the second only a few capillaries were visible at room temperatures. With rise of environmental temperature a slow increase in the rate of flow occurred and a few more capillaries became visible.

In *arteriosclerosis* the density (area of visible blood) of the capillary bed on the forearm is not abnormal but the rate of flow is frequently decreased.⁶¹

Some studies^{28, 35, 49} have been made which show that in a general way capillary development in the skin may be inhibited in mentally deficient individuals.

Capillary pulsation has been considered a sign of *aortic insufficiency*. Crawford's cinematographic observations on the capillaries in the nail fold made simultaneously with an electrocardiogram failed to show propagation of the arterial pulse wave along the capillary wall in patients with aortic insufficiency. Landis³³ has occasionally observed variations in capillary pressure with the pulse in normal subjects and quotes³⁴ Hurtle as having seen rhythmic increases in capillary blood flow during cardiac systole. The observations of Crawford on the one hand and of Landis and Hurtle on the other are not necessarily contradictory but do indicate that the mechanism involved in the clinical phenomenon called capillary pulsation is not clear.

It should perhaps be recalled that the phenomenon may be observed in a warm normal subject as well as in the patient with aortic insufficiency.³⁷

In *urticaria*, *insect bites* and *herpes zoster* the local skin lesion is due to the temporary increase in permeability of the capillary wall permitting the passage of fluid into the surrounding tissues.

It is evident from the foregoing review of clinical conditions in which the capillary circulation is involved that as yet knowledge of the subject is fragmentary and quite incomplete. With the development of better

means of studying the capillary circulation from all angles in health and disease will come a greater appreciation of the importance of this portion of the circulatory system

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CHAPTER XLV

VENOUS PRESSURE

By H. G. SCHLEITER, M.D.

Venous pressure readings with only minor exceptions reflect the functional efficiency of the right side of the heart. A normal right heart will respond to an increasing venous load by increased response in heart rate and stroke volume so that the venous pressure tends to be equalized and remain at a normal level. When an insufficient right heart cannot respond to an increased venous load, the pressure in the systemic veins rises to abnormal levels. If the pressure remains sufficiently high, the characteristic manifestations of right heart failure take place such as visible engorgement of the superficial veins, particularly in the neck, enlargement of the liver and accumulation of fluid in the body spaces and tissues. It is obvious that these clinical manifestations depend on a single factor—namely, an abnormally great venous load. The importance of measuring this venous load, or venous pressure, becomes evident. Before considering further the factors which influence venous pressure, it seems advisable to consider first the principal methods of estimating venous pressure. There are three ways of doing this: (1) By observation and palpation of the peripheral veins; (2) by recording on a manometer the point at which a peripheral vein will collapse under pressure; (3) by inserting a needle into a superficial vein and recording the pressure either in terms of a column of blood or a column of fluid, such as salt solution which is in communication with the venous blood flow.

Whatever method is employed the patient should be at rest in the recumbent position for 15 minutes to one half hour before the determination is made, and he should lie with his head in line with the body, or as nearly so as his condition will permit. The vein which is used for the determination (usually the antecubital vein) should be on a level with the right auricle. This may be done by having the arm resting on a cushion so that the anterior surface of the arm (the zero point of the

manometer) is 10 cm above the bed.¹ The arm should also be extended somewhat away from the body, about 15 degrees. The arm and chest should be free of clothing.

The first method is referred to above consists in raising the arm slowly at the side and noting the height above the sternum at which the veins on the dorsum of the hand will collapse. The junction of the left

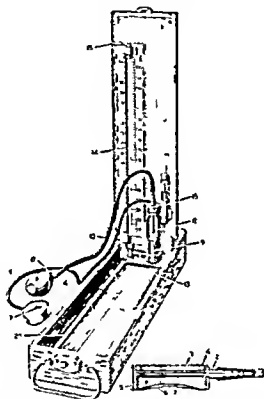


FIGURE 1. Indirect venous pressure manometer of Horder and Fyster (Foster).
Foster (Cyclopedia of Medicine F. A. Davis Co.)

fifth costal cartilage with the sternum is taken as the reference point.² This method can do no more than give a very rough idea of the pressure where the latter is quite exaggerated. If no other method is available it may at times be of use, but should not be considered comparable to the second and third methods mentioned above.

Indirect Method: The indirect method of estimating venous pressure is best exemplified by the apparatus of Horder and Fyster.^{2,3} It makes use of a small metal air chamber, covered with a glass disc, which is fastened over a vein of the hand or forearm.⁴ This chamber is connected with a water manometer to which the patient is connected.⁵

bulb. Sufficient air is pumped into the chamber to collapse the vein under observation. The height at which the water in the manometer stands at the moment of collapse represents the venous pressure reading. Where the veins are clearly visible this method is satisfactory and accurate. However, where the veins are not clearly visible it becomes difficult and is also subject to personal error.

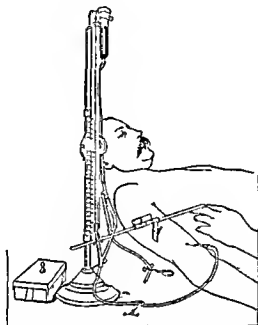


FIGURE 2 Direct method of Moritz and von Tabora
(Cyclopedia of Medical and Dental Sciences Co)

Direct Method (a) The method of Moritz and von Tabora⁴ consists of a needle of sufficiently wide caliber (18 gauge) connected by means of a piece of Y tubing to an upright manometer and to a container holding normal saline solution (Fig. 2). The zero point of the manometer is placed at 10 cm above the level of the bed and the arm rests on a cushion as described above. The needle is inserted into a vein at the bend of the elbow and saline solution permitted to enter from the manometer. The point in the manometer at which the saline stops flowing represents the venous pressure level. This method is accurate and has the advantage that readings may be made over a number of hours at a time if desired since the blood does not tend to clot in the needle.

A simpler method and one quickly applied measures the column of blood directly. An L shaped calibrated glass manometer is connected by

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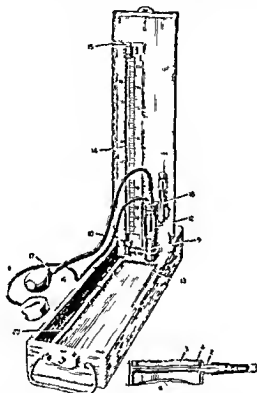


FIGURE 1. Direct venous pressure manometer of Harker and Eyster, redesigned by Fester. (Copyright of Medical Electric Supply Co.)

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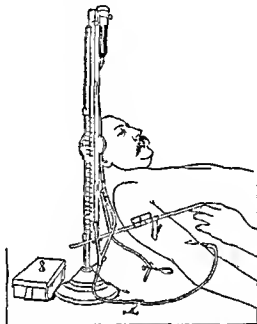


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A simpler method and one quickly applied measures the column of blood directly. An L-shaped calibrated glass manometer is connected by

means of a sufficiently wide needle (18 gauge) to the blood within a vein.⁵ The bore of this tube is 1 mm. The readings are made in terms of a column of blood (Fig. 3). This, compared with the column of saline, involves an error of not more than 0.5 cm., so that with this reservation the readings by this method and by that of Moritz and von Tabora are comparable. The cuff of a standard sphygmomanometer is loosely applied to the arm, well above the elbow, and the skin at the bend of the elbow cleansed with iodine and alcohol. The veins if not distinctly visible are now made so by inflating the sphygmomanometer cuff to a pressure of 10 to 15 mm. of mercury. The needle attached to

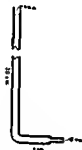


FIGURE 3 Direct manometer for measuring venous pressure in terms of centimeters of blood (Cyclopedia of Medicine, F. A. Davis Co.)

the manometer is inserted into the vein and the cuff pressure immediately released by opening the outlet valve. The constriction of the cuff is thus removed before the blood has reached the elbow of the glass tube. When the column of blood has ceased rising in the tube the reading is taken. The entire procedure is completed in less than a minute.

In order to insure the correctness of the reading and the patency of the needle, the cuff is now slightly inflated, so as to make the blood rise still higher in the tube. The cuff is then deflated and the needle immediately removed to prevent a return flow of blood. In order to prevent possible coagulation of the blood it has been recommended by Oppenheimer and Hitzig⁶ that the manometer and needle should first have their lumen rinsed with ten per cent sodium citrate solution. The entire process requires practically no more time than an average estimation of arterial blood pressure. In 50 normal patients, the venous pressure by this method varied between 1 and 11 cm., the majority of the figures ranging between 6 and 8 cm. It is not usually necessary to take readings

more than once a day. The amount of blood lost during a reading is negligible—1 to 3 cc.

Oppenheimer and Hitzig⁶ likewise call attention to the value of observing the effect on venous pressure produced by compression over the right upper quadrant of the abdomen for a period of about one minute. In normal individuals the temporary increase of venous return to the right heart is readily handled by the competent myocardium and the venous pressure level in such individuals either remains stationary or eventually falls progressively from 0.5 to 2 cm. In incipient right heart failure in which the initial venous pressure is either normal or slightly elevated a rise of 1 to 3 cm. may occur after one minute of right upper quadrant compression. In frank right heart failure in which the initial venous pressure is considerably elevated above the maximum normal a rise of 5 to 20 cm. above the original level of venous pressure may be obtained after right upper quadrant compression. This procedure is of clinical value since it demonstrates the inability of the right ventricle to take care of the temporary increase of venous return. This phenomenon is not referable solely to the liver but can be produced also by compression of the lower abdominal quadrant—thus indicating that the temporary increase of venous return is due to elevation of intra-abdominal pressure rather than to a specific liver phenomenon.

Venous Pressure Under Normal Conditions. The force of gravity and muscular exertion having a marked influence on venous pressure these factors should be excluded by having the patient resting in the recumbent position. Under these circumstances venous pressure is dependent chiefly on two factors: (1) The pressure remaining in the small veins after the blood has passed the capillary field and (2) the effectiveness of cardiac contractions. The pressure in the small veins is regulated by the degree of arterial pressure and by the extent to which the capillary field is open. The normal heart muscle is capable of responding within wide limits to varying quantities of venous blood and therefore of maintaining the venous pressure at a normal level.

The extent of cardiac work during contraction is determined by the amount of blood in the ventricles, i. e. the intraventricular pressure. The pressure in the ventricles depends on the intramural pressure and the latter in turn is caused by the pressure of blood in the great veins. If the pressure in the great veins is excessive the normal heart responds

by more vigorous contractions and therefore propels additional blood into the arterial tree. The degree of venous load therefore determines the amount of work to be done by the right heart.

In a normal individual at rest the venous pressure varies between 4 and 11 cm of water.⁷ Like arterial pressure venous pressure is subject to diurnal variations and in the healthy individuals tends to be lowest during sleep. On the other hand in cardiac insufficiency the venous pressure is highest during the sleeping hours. Age has been found to have no influence so long as the subject is in the recumbent posture. In the sitting posture the pressure appears to rise with age.⁸ This fact emphasizes the necessity of the recumbent posture in making determinations. Under experimental conditions the human heart has been found capable of responding to a venous pressure as high as 60 cm without signs of overstrain. However when the heart reserve is reduced a pressure as high as 20 cm may be an indication of serious danger.

Venous pressure is subject also to respiratory influences. During inspiration the increased negative pressure in the thorax causes a greater emptying of the large veins with a fall in venous pressure. The contrary occurs during expiration. In health the effect of the normal respiratory phases on venous pressure is not significant. Conversely excessive respiratory efforts associated with overventilation of the lungs result in a definite lowering of venous pressure. Holding the breath results in a rise of pressure. Thus marked rises are seen in seizures of bronchial asthma in the course of the Valsalva experiment and in the apneic periods of Cheyne Stokes breathing. During the induction of anesthesia there is a rise of venous pressure which is occasioned by muscular activity and by an increase of carbon dioxide in the blood.⁹

RELATION BETWEEN VENOUS PRESSURE AND CEREBROSPINAL FLUID PRESSURE

Except for slight variations it has been found that venous pressure and cerebrospinal fluid pressure run closely parallel to one another. This is for the reason that the cranium and cerebrospinal canal represent a rigid chamber. Rises of venous pressure within these cavities cannot cause a displacement of cerebrospinal fluid and thus therefore undergoes a pressure rise corresponding to the increase of venous pressure. The usual ratio of cerebrospinal fluid pressure to venous pressure is about 1.6 to 1.¹⁴

This fact is of considerable clinical importance in certain cases of total heart failure associated with coma and Cheyne-Stokes respiration. Under such circumstances a prompt relief of the cerebral symptoms may be produced by a spinal tap in preference to or preliminary to venesection.

CASE REPORT. A white male of 63 years was admitted to the Allegheny General Hospital with syphilitic aortitis and greatly enlarged heart. On admission he was suffering from advanced total heart failure, the signs of right heart failure being particularly pronounced with marked engorgement of the veins of the neck, hepatic enlargement and edema of the lower extremities. Shortly after admission he lapsed into a comatose state with pronounced Cheyne-Stokes breathing, and his death seemed imminent. The venous pressure by the direct manometer method registered 26 cm. of blood, the spinal pressure was 40 cm. A spinal tap was performed and the patient rapidly improved, so that by the next morning he had regained full consciousness. Further treatment followed, consisting chiefly of digitalis and theobromine. Clinical improvement proceeded uninterruptedly so that after a few weeks he was able to be up and about and even assisted in some of the lighter ward duties. He continued in relatively good condition for about three months, when he had another attack of heart failure, this time not associated with cerebral symptoms to which he succumbed.

RELATION BETWEEN VENOUS AND ARTERIAL PRESSURE

Some observers are of the opinion that arterial pressure and venous pressure levels are independent of each other and of resistance in the capillary bed; they conclude that an elevated venous pressure invariably means cardiac failure independent of the cause of failure or the associated disease.⁷⁻¹⁰ Others have believed that there is a certain parallelism between the two, even going so far as to suggest a mathematical relationship between the normal venous pressure in centimeters of water as compared with the normal systolic arterial pressure in millimeters of mercury, the ratio being 1 to 13. According to this idea an arterial pressure of 130 mm. would correspond to a venous pressure of 10 cm. of water,¹¹⁻¹² and a pressure of 220 mm. to a venous pressure of 17 cm. without the necessary presence of heart failure. However, the problem is not so simple as this, nor the mathematical relationship by any means so exact, even in the normal. At the same time there is reason to believe that a venous pressure several centimeters higher than the maximum normal may under certain conditions be associated with normal heart action.

Villaret and his associates¹² believe that certain cases of essential hypertension are accompanied by an elevation of venous pressure. This elevation of venous pressure they attribute to the high arterial pressure transmitted through the capillary field because these cases showed no evidence of cardiac failure. Where the venous pressure exceeded the ratio of 1 to 13 previously mentioned it was attributed to cardiac insufficiency. Certain cases of arterial hypertension were found with a normal or low venous pressure. Thus they concluded was due to the increased resistance of the capillary field caused by sclerosis. The findings of these investigators have not been confirmed by certain other observers^{17 18 19} who believe the venous pressure to be independent of capillary pressure. However it appears that a venous pressure several centimeters above the maximal normal may occur in association with high arterial pressure even if cardiac failure is not present.²⁰ Roky and Klein²¹ in 60 cases of arterial hypertension found the venous pressure above the maximal normal in over ten percent. These cases presented no evidence subjective or objective of heart failure. The venous pressure readings in these cases varied between 14 and 16 cm. The remaining cases of arterial hypertension showed a normal venous pressure reading.

A satisfactory explanation of these variable relationships in the absence of heart failure has not been presented. However it appears that in certain cases of essential hypertension there is an elevation of venous pressure which must be referable to some factor or factors aside from the heart -- Eyster and Meek²² in venous pressure experiments in dogs report that certain stimuli which cause a rise of arterial pressure such for example as an increase of intrathoracic pressure or an injection of adrenalin produce moderate or slight rises of pressure in the jugular and iliac veins. It has been noted that in hemiplegia the sound side showed a high arterial pressure with a normal venous pressure while the paralyzed side with the same high arterial pressure, showed a venous pressure somewhat below normal. This suggests a deficiency in the peripheral circulation on the diseased side with a reduced tone of the arterioles. It was also noted in an instance of Raynaud's disease²³ without heart insufficiency that there was a slight rise of venous pressure. In this case there were varicose distentions of the capillaries with a local alteration in the contractility of the arterioles.

It seems therefore in view of the above that a retrograde obstruction such as increased pressure in the right auricle without manifest heart insufficiency does not always provide an adequate explanation of an elevated venous pressure and it seems possible under these circumstances that a change in the tonus in the veins may be responsible for the venous pressure rise. There is considerable lability in the small arterioles. As result of this lability great fluctuations in arterial pressure may occur within a short time in some cases of hypertension. In other hypertensives where the contractility of the arterioles is lessened by pathologic changes the arterial pressure is more constant consequently hypertensive patients with labile arterioles may have rises of venous pressure while those cases in whom pathologic changes have become fixed and offer more obstruction to the outflow from the arteries may be associated with normal or even slightly lowered venous pressure.

Physical exertion has little or no effect on venous pressure in the healthy. Where there is clinical insufficiency venous pressure rises after exertion the extent of the rise tending to be in proportion to the degree of insufficiency. This rise varies from 2 cm. in mild cases to 7 cm. or more in severe cases.¹⁶ On cessation of exercise the return to normal is immediate in the healthy but is delayed where there is decompensation. This applies particularly to the maximal arterial pressure and to the venous pressure the return of diastolic pressure to its previous level being rapid in all cases.²⁴

In observing venous pressure it is essential as in the study of arterial pressure to be guided by a series of readings rather than by a single estimation. Under these conditions a consistently rising level of venous pressure is suggestive of cardiac failure a consistently falling pressure with clinical improvement, regardless of the actual height of the readings. In the presence of acute heart failure a single reading above 20 cm. is undoubtedly of the greatest importance particularly in deciding on the advisability of venesection. However before considering venesection it is necessary that the subjective and objective signs of heart failure be present and that the elevated venous pressure should not be caused by some extracardiac source of venous obstruction for example a collection of pleural fluid or an intrathoracic tumor may cause pressure on the great veins causing a rise of venous pressure, and such factors should be excluded in considering diagnosis and treatment.

CARDIAC INSUFFICIENCY

Aside from severe emphysema and intrathoracic conditions producing pressure on the great veins the only clinical state which will cause a well marked rise in systemic venous pressure is failure of the right side of the heart (the vascular conditions previously referred to as being independent of heart failure are associated only with nonsignificant rises in venous pressure). Failure of the right side of the heart may be of two types: functional failure and failure from structural lesions which interfere mechanically with filling of the right ventricle. The overwhelming majority of cases of right heart failure represent the functional type due to increased pressure in the pulmonary circuit which in its turn has resulted from left sided failure. A less common but not infrequently encountered type of functional right heart failure is that due to pulmonary hypertension which has resulted from deformities of the chest or from extensive obliteration of the vascular bed of the lungs as the result of various chronic diseases. It has been found however that pulmonary hypertension due to such causes will not bring on right heart failure unless 60 per cent or more of the vascular pulmonary bed is obliterated.

The mechanical lesions which interfere with filling of the right ventricle and thus give rise to markedly elevated venous pressure are tricuspid stenosis, excessive fluid in the pericardial cavity and constrictive pericarditis. Of these the condition most frequently encountered is constrictive pericarditis.

When extensive elevation of venous pressure is due to functional or intrinsic right heart failure the pressure waxes and wanes with the state of the patient.²⁵ On the other hand when a structural or mechanical cause is responsible the venous pressure is sustained at the same high level. This is notably the case with a constrictive pericarditis.

As previously mentioned the normal heart muscle is able to respond within wide limits even to excessive degrees of venous load. However if the cardiac muscle becomes incompetent it cannot handle even a normal venous load. In such a case the venous pressure rises; this is followed by dilatation of the heart, engorgement of the peripheral veins, enlargement of the liver, transudation into the serous cavities, edema of the extremities and a diminished excretion of urine. It has been shown that there is an inverse ratio between venous pressure and urine excretion. In cases where failure is limited to the right side of the heart dyspnea

is not likely to be marked. On the other hand there is a tendency to rapid heart action. There are various processes concerned in the accumulation of fluid in the body tissues—such as lowered osmotic pressure in the blood plasma, increased permeability of the capillary walls and increase of capillary pressure secondary to a rise in systemic venous pressure. In edema associated with cardiac lesions the chief of these factors is the increase in intracapillary pressure.

A progressive rise above the normal figures for venous pressure (4 to 11 cm. of water) indicates the development of heart failure. In order to show such a progressive rise repeated readings are necessary; conversely where clinical heart failure is present a consistently falling venous pressure is indicative of clinical improvement. So far as a single reading is concerned, if it be above 20 cm. it is evidence of marked cardiac failure if the clinical signs of heart failure are present. However in the stages below 20 cm. single readings may not be conclusive and it is here that serial readings are of particular diagnostic value.²⁷

VENESECTION

In right heart failure a rising venous pressure or a venous pressure of 20 cm. or more presents an indication for venesection. Often venesection is followed by a progressive fall in venous pressure. In the normal individual venesection results in only slightly and transitory changes of venous pressure. However in cardiac failure with elevated venous pressure the removal of a significant amount of blood (500 cc. on the average or between 3 and 4 cc. per pound of body weight) will temporarily lower the venous pressure so that if the heart has a sufficient margin of reserve it will respond to the lowered load which has been thus rapidly produced and by more efficient contractions continue to maintain the lower pressure which has been produced by venesection. The venous pressure will steadily fall and the signs of heart failure diminish; dyspnea becomes lessened, the surface area of the heart diminishes, the urine output rises and edema of the extremities disappears. If the response is inadequate the temporarily lowered venous pressure will rapidly regain its previous level.

In an individual of average weight the removal of 500 cc. of blood or 3 to 4 cc. per pound of body weight is usually enough to cause a decisive lowering of pressure. Less than this is likely to cause the vene

section to fail of its purpose. The object of a venesection is to remove a material amount of burden on the right heart in as short a time as possible. It will not do to remove 250 or 300 cc. of blood on one day and then a similar amount the following day, since the total load must be removed at one time in order to provide an adequate opportunity for the heart to recover. If the venous pressure response to venesection is favorable it need not be repeated unless another crisis arises at a later date. If the response to venesection is not favorable further venesections are not likely to produce any benefits.

In those cases in which an extensive venous pressure rise is due to mechanical obstructions such as constrictive pericarditis the venesection will produce only the most temporary benefits if in fact it is not futile since here the cause of the obstruction should be removed where possible. As a rule a satisfactory venesection may be performed by inserting a needle into a vein and allowing the blood to flow. At times the use of a syringe may be of aid if the flow is not satisfactory. If even with a syringe a sufficient amount of blood is not obtained an incision should be made and the vein opened. Prior to performing a venesection one should be assured as to the hemoglobin content of the blood. A moderate degree of anemia should not be a hindrance if venesection is urgently needed. However if the hemoglobin is below 70 per cent the patient may suffer as much from blood depletion as he will gain from venesection.

The question may arise as to whether in right heart failure a venous pressure above 20 cm. constitutes an inescapable indication for venesection. This is not necessarily the case. We have seen patients with pressures as high as these improve with drug therapy, restricted diet and decrease of fluid intake without venesection. There is little doubt however that where the pressure is high and the symptoms are urgent an adequate venesection is likely to give the patient a better running start to recovery. Before venesection is considered or in fact a venous pressure reading taken one should be quite sure that any material accumulations of fluid in the thoracic or peritoneal cavity have been removed.

It has been noted with interest that many writers in discussing the treatment of acute pulmonary edema which represents a form of left-sided heart failure recommend venesection as one of the measures for the relief of this condition. It is difficult to understand just why this

should be, unless the venous pressure in such instances is elevated which is usually not the case

It should not be forgotten that unless the venous pressure is very high the trend of venous pressure is more important than a single reading. If the trend is upward and clinical signs and symptoms of heart failure are present, venesection will be more successful if done promptly than if delayed until the cardiac reserve has been exhausted.

It has been repeated a number of times in this chapter that with certain infrequent exceptions a markedly elevated venous pressure is an indication of right heart failure either functional or mechanical. In other forms of heart disease in which the right heart is not implicated, venous pressure will not show any material deviations from the normal. Conditions associated with rapid heart rate do not involve a rise of venous pressure unless for some reason the right side of the heart is involved. Such conditions are hyperthyroidism, paroxysmal tachycardia, auricular fibrillation and auricular flutter. If the rapid heart rate continues over a long period of time such as weeks or months, the right heart may give way and under such circumstances the venous pressure will rise.

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CHAPTER XLVI

SHOCK

By NORMAN E. FREEMAN, M.D.

Introduction The nature of shock is a subject which has been confused by an attempt to bring within one category all conditions characterized by a low blood pressure. This attempt was natural since one of the outstanding accompaniments of shock is the low and falling blood pressure. Cannon¹ has stated that low pressure is probably the central feature or one of the most essential features of shock. With the paramount importance of diminished blood pressure in mind classifications were made to differentiate the various types. Shock was defined in terms of primary and secondary shock on the basis of the time of its onset. Others defined shock in terms of the initiating causes such as histamine shock, shock from burns, shock from peritonitis and traumatic and surgical shock. In one of the more complete classifications recently brought forward Harrison² has classified shock under the terms hemotogenic, neurogenic and visogenic. These classifications have in assumption in common namely that shock is essentially a condition of low blood pressure. The issue is confused if shock is more than a state of lowered arterial pressure. It is necessary to recall the classical picture of shock in order to ascertain whether or not there is more of significance than the reduced blood pressure.

The patient in shock has the appearance of being seriously ill. The significant features are centered about the peripheral circulation. The skin is cold and moist. The pulse is feeble and rapid. There is usually a lowered blood pressure and the patient presents the picture of weakness bordering on exhaustion. This condition is not sudden in onset but requires time for its development. If untreated there is a steady decline to a fatal termination. During the downward course there is progressive enfeeblement and gradual suppression of all the bodily functions. With this picture in mind it is clear that low blood pressure is not the only feature of significance. Here is the time factor. Low

pressure itself is not necessarily fatal but if the reduced blood pressure is maintained for a period of time, shock may be produced. Again the progress of the shock is of significance. Shock cannot be diagnosed simply by a single determination of blood pressure. It is the course of the blood pressure rather than the isolated reading which is important. Shock will therefore be defined in terms to indicate that it is a process rather than a static condition.

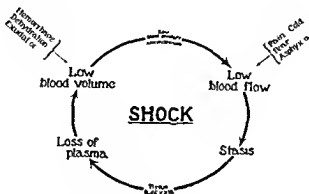


FIGURE 1 The process of shock (Freeman Pennsylvania M J)

DEFINITION

Shock is the clinical condition characterized by progressive loss of circulating blood volume brought about by the tissue anoxia which results from inadequate circulation.

In this definition which is illustrated in Fig. 1 there are four points which require discussion. The reduced blood volume, the progressive nature of the loss, the tissue anoxia, and the inadequacy of the circulation.

1. Is There Always a Diminished Blood Volume in Shock? The brilliant researches of Robertson and Bock³ and Keith⁴ during the World War of 1914 to 1918, showed clearly that a reduced blood volume was the cause for the reduced blood pressure in shock. It is generally agreed today that there is a reduction of the circulating blood volume in shock.

2. Is the Loss of Circulating Blood Volume Progressive? Hemocentration in the process of shock was first described by Cannon, Fraser and Hooper.⁵ This concentration is more evident in the peripheral regions than in the central circulation. Recent studies by Moon⁶ have supported the earlier observations. There is general agreement on

the significance of progressive hemoconcentration as shock is developing. This concentration indicates loss of plasma volume.

3 Is There Tissue Anoxia in Shock? One of the characteristic observations on clinical cases of shock has been the subnormal temperature. Studies of the oxygen utilization in experimental animals during the process of shock⁷ have demonstrated a serious reduction in the bodily metabolism. Direct study of tissue anoxia has not been made but the inferences drawn from examination of the blood are suggestive. Acidosis is well recognized as a feature of shock. It is considered to be

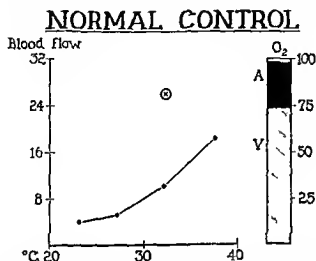


FIGURE 2. Blood flow in normal control. In this as in the following figure the solid line shows the effect of increasing temperature of 1 and on blood flow through the hand. Cross surrounded by circle indicates blood flow 30 seconds after release of tourniquet which has been applied for five minutes. Column at right indicates oxygen saturation of A the arterial and V the venous blood taken from that hand. Ordinate—blood flow. Abscissae—degrees centigrade. (Freeman, Pennsylvania M. J.)

an expression of the tissue anoxia. The reduced oxygen content of the venous blood gives further evidence of the impaired oxygenation of the tissues. This condition was first described by Aub and Cunningham⁸ and subsequent studies by Block and Bradburn⁹ and Freeman, Shaw and Snyder¹⁰ have given support to this concept. Apparently shock is associated with a severe degree of tissue anoxia.

The precise nature of the changes physical and chemical brought about by tissue anoxia and in what manner these changes produce an increase in permeability of the capillaries is not known. Certain of the

recognized alterations will be taken up in the discussion of the chemistry of shock.

4 **Is There Reduced Circulation in Shock?** The significance of inadequate circulation in shock was clearly stressed by Erlanger, Gesell and Gasser¹¹ at the close of the World War. Studies by Gesell¹² on the effect of hemorrhage and tissue abuse on peripheral blood flow further strengthened this concept. Investigations illustrated in Figs. 2 and 3 on the peripheral blood flow through the hand in clinical cases of surgical shock by Freeman, Shaw and Snyder¹⁰ suggested the etiology

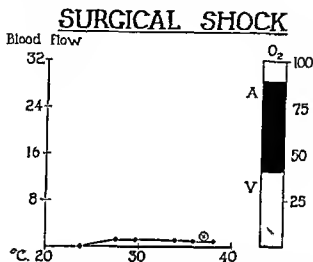


FIGURE 3. Blood flow in surgical shock. This patient had been operated upon for intestinal obstruction four hours previously. A cecostomy had been performed under local anesthesia. At the time of observation she was in clinical shock with a normal temperature, cold clammy skin, a pulse of poor volume with a rate of 130, and a blood pressure of 80/60. She succumbed in spite of repeated transfusions six hours after these observations were made. (Freeman, Pennsylvania M. J.)

cal significance of inadequate circulation in the production of shock. Blalock and Levy¹³ observed that the circulation was reduced although not to as great a degree in other regions of the body in this condition. Investigations in the laboratory have thus confirmed observations in the clinic that there is a serious reduction in the distribution of blood to the tissues of the body during the course of shock.

CLINICAL PICTURE

The clinical picture of shock is determined by two considerations:

1. The physiological responses of the body to the initiating causes and
2. The bodily reactions to failure of the circulation.

1 The initiating causes of shock are numerous in the broad sense. They subject the organism to harm or to the prospect of injury. Whether the initiating factor be dehydration, trauma or emotional distress, there is a threat to the survival of the individual. The sympathetic nervous system, as Cannon¹⁴ has pointed out, is specifically designed to cope with an emergency and is called into play by stimuli which threaten the integrity of the organism. Such factors as cold, pain, asphyxia, fear, hemorrhage, infection and dehydration have been found to be strong stimulants of sympathoadrenal activity. In this manner the original cause of the shocklike condition calls forth activity of the sympathetic nervous system. These evidences of sympathetic activity are to be found in the increased pulse rate, the pallor of the skin, the sweating, the pinched throat and the suppression of gastrointestinal activity.

2 As soon as there has been some alteration in the internal environment of the body, as for instance by acute loss of blood from hemorrhage, certain mechanisms are called into play to readjust the organism to the defect. There is acceleration of the pulse and vasoconstriction to maintain the level of the falling blood pressure. The blood is diverted from the nonessential parts of the body, such as the skin and the intestinal tract, to the vital organs. These reactions may be called purposeful in that they are designed to fit the body to meet the emergency. The clinical picture of shock is thus in part an evidence of the reaction which the organism is making to adjust to the changes in its internal environment.

When the stage of failure has been reached, the clinical picture becomes more precise. At this stage there are combined the evidences of the body's reaction to the initial trauma with evidences of inadequate circulation to the tissues. As a result of general impairment in the supply of blood to the tissues, with consequent tissue anoxia, there is progressive acidosis. With the failure of the peripheral circulation, there is evidence of concentration of the blood in the capillaries and venules. Unless hemorrhage has played a major part, there is usually cyanosis of the skin and mucous membranes. Hemoglobin, hematocrit or red blood cell determination of the peripheral blood show evidence of concentration of the formed elements. There is suppression of renal function with retention of nitrogenous waste products. Gastrointestinal function is inhibited with resultant distention and paralytic ileus. The progressive reduction

of the circulating blood volume leads to a falling blood pressure and a rising pulse rate the unmistakable signs of shock. Failure of the circulation is associated with cessation of salivary flow and intolerable thirst. The mental faculties gradually become clouded until the patient sinks into stupor which merges imperceptibly with death.

PATHOLOGY

Shock is the final phase of many clinical conditions characterized by prolonged impairment of the circulation. The pathological picture of shock is usually complicated by that of the initial lesion which produced the process. In this discussion emphasis will be placed only upon those features which belong essentially to shock.

In his investigations on the mechanism of hemorrhagic infarction Welch¹⁵ made the significant observation that reduction in the arterial pressure in the mesentery of the dog produced stasis with concentration of the blood corpuscles in the capillaries and veins of the loop of intestine supplied by the artery which was compressed. He could observe no change in the appearance of the vessel walls but found that the forward movement of the blood was checked and that stasis soon took place. Landis¹⁶ in his observations on the mesentery of the frog analyzed this reaction more closely and found that although no changes might be visible in the blood vessel walls there was an increase in the permeability of the endothelium so that plasma escaped and left the cells stranded. These facts have been confirmed by a number of observers and appear to be well substantiated. It is the opinion of the majority of investigators who have worked in the field of shock that this increase in the permeability of the minute blood vessels in consequence of impaired circulation is the central feature in the process of shock. The pathological picture which is found when the tissues are examined after death from shock is that to be expected from peripheral circulatory failure. There is widespread congestion and engorgement of the capillaries and venules throughout the body.

Such a picture was found by Gross, Erlanger and Meek¹⁷ in shock experimentally produced in a variety of ways. They observed in the intestinal mucosa that the capillaries and small veins are greatly dilated and tightly packed with red blood cells. More recent studies on the pathology of shock by Moon¹ have corroborated their observations. This congestion

from stasis is found throughout the viscera and in the lungs. There is edema in the tissue spaces and effusion in the serous cavities. If the impaired circulation has persisted in the experimental animal for sufficient time there may be actual necrosis of the intestinal mucosa¹⁸ as shown in Fig. 4. The ultimate pathological picture of shock may in reality be ascribed to death of the peripheral tissues before that of the body as a whole.



FIGURE 4. Microscopic appearance of the duodenum of a dog in which shock had been produced by low blood pressure of six hours duration brought about by graded hemorrhages. The superficial portions of the mucosa had disappeared. (Freeman Shaffer Scheeter and Holling, J. Clin. Investigation)

PHYSIOLOGY

The physiology of shock is determined by the reactions of the body not only to the initiating causes but also to the reduction of circulating blood volume which represents the underlying feature of shock. For purposes of convenience these reactions will be grouped under the different organ systems.

Cardiovascular. There is sympathetic stimulation of the cardiovascular system throughout the course of shock, no matter in what manner the process is brought about. This stimulation is to be observed in the increase in pulse rate and the peripheral vasoconstriction. The character of the pulse is of great significance in the clinical estimation of the condition of shock. Its volume probably gives the single best

indication of the general condition of the patient. The contrast between a full radial artery which indicates an adequate output of the heart and a weak "thready" pulse of poor volume differentiates a blood pressure associated with a normal cardiac output from an identical blood pressure maintained by peripheral vasoconstriction in the face of a diminished circulating blood volume. Johnson and Blalock¹⁹ have shown that the cardiac output declines well before the blood pressure as shock comes on. It may be said categorically that there is always an increase in pulse rate in shock unless there is direct or reflex cardiac inhibition. Failure in cardiac response may be intrinsic since it has been shown that in experimental²⁰ and clinical²¹ dehydration, there may be such impairment of blood supply to the heart itself that full tachycardia is not observed. The cardiac inhibition may also be reflex through vagal stimulation as in increased intracranial pressure.

Vasoconstriction is also a regular accompaniment of shock. This constriction is more marked in the peripheral portions of the body (Freeman, Shaw and Snyder¹⁰) than in the central areas (Blalock and Levy¹³). In the early stages, particularly in the presence of fever and infection, the blood flow through the peripheral portions may actually be increased. It seems likely that this hyperemia is due to the vasodilatation which represents the body's effort to dissipate heat. In the later stages of shock, there is always marked peripheral vasoconstriction in spite of an elevated temperature.

The blood pressure is generally low in the early stages of shock, especially if there has been loss of blood or plasma. When the condition is being produced without original impairment of the cardiac output, the blood pressure may be normal or even increased. The state of the peripheral circulation is of greater significance than the blood pressure. In the words of a surgeon of wide experience, "I'd rather see pink ears than an elevated blood pressure." In the terminal stages, the blood pressure is always reduced, and the degree of reduction bears a close relationship to the severity of the shock.

Gastrointestinal: Stimulation of the sympathetic nervous system brings about inhibition of function in the gastrointestinal system, and the signs of shock in this system are expectedly those of decreased activity. The salivary flow is suppressed with resultant dry mouth and parched

throat. Peristalsis is diminished and paralytic ileus may be produced. The reduction of circulation in the intestinal tract is frequently associated with injury to the mucosa so that superficial ulceration may be found with free blood inside the lumen. There may be injury to the liver from the prolonged anoxia as shown in Fig. 5. This damage may give rise to widespread bodily changes. Even though the patient may respond well to remedial measures as far as the circulation is concerned the splanchnic inhibition will frequently present a major complication.

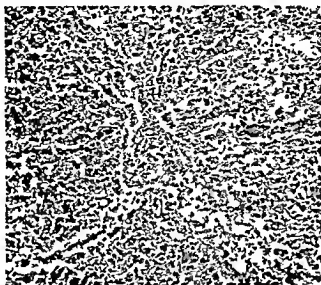


FIGURE 5. Microscopic appearance of the liver of a dog in which shock had been produced by low blood pressure of six hours duration brought about by graded femoral ligation. The liver cells showed degeneration and necrosis (Freeman, Shaffer, Scheeter and Hollings: J. Clin. Investigation).

Genitourinary. The reflex vasoconstriction does not spare the kidneys as the typical suppression of renal function indicates. There is retention of nitrogenous waste products. The urine is concentrated and contains albumin, red blood cells and casts although after the patient has recovered there may be no evidence of permanent renal damage. Occasionally the suppression of renal function may be so severe that anuria results. This anuria may persist long after the patient has recovered from the circulatory crisis.

Neuromuscular. Although there is no impairment of muscle power the patient in shock exhibits great weakness and prostration. There is a disinclination to move. As the stage of decompensation is reached

the extremities become cold and the muscles feel doughy to the touch. The sensorium is clouded although the individual may be conscious to the end. Reaction to painful stimuli, both in clinical and experimental shock is lessened. The psychic response seems to be one of apathy although on closer observation the apparent lack of interest in the surroundings may be found to be the result of a state of abject terror. The patient is paralyzed with fear. Death is staring him in the face and he cannot look away.

There is frequently dilatation of the pupils and there may actually be exophthalmos. The wide staring eyes, restlessness and "over bright" appearance of the patient with peritonitis are signs which are to be viewed with alarm.

The skin is usually moist and cold and has been termed clammy, to suggest the similarity to the sensation of touching dead flesh. The death of Falstaff is graphically described by Mistress Quickly "then I felt to his knees, and they were as cold as any stone, and so up'ard and up'ard, and all was as cold as any stone." Cyanosis is present in the nail beds and the skin of the abdominal wall may exhibit a blotchy appearance. When the finger tip is pricked to obtain blood for study, there slowly exudes a dark viscous fluid. If an incision be made, the wound does not bleed except for a slow trickle from the veins. The blood is dark. The muscles appear brown and desiccated. In the sphincter area the arteries are seen to be contracted to fine threads and the veins show up more prominently as darker ribbons. There seems to be a general loss of tone in the voluntary muscles.

When dehydration is associated with shock, the skin is dry and cyanosis is more apparent. When pinched into a fold the wrinkle will persist. The eyeballs are soft and the eyes sunken in the sockets. The tongue is dry and red and the mucous membrane of the mouth glazed.

Respiration: If hemorrhage has been a major factor in the production of shock, the respiration is generally of the sighing type with occasional deep yawns. Otherwise, the breathing is frequently suppressed both in depth and frequency. As the later stages of shock approach, with the attendant acidosis, the respiration is increased and may be quite rapid. In the terminal stages, the respiratory center is more and more depressed until the breathing finally ceases.

CHEMISTRY

No chemical substance capable of producing shock has yet been consistently demonstrated in the circulating blood in sufficient quantity to be generally accepted as the cause of shock. There are many substances on the other hand which can produce shock when injected into the blood stream. Histamine, peptone, muscle extract, intestinal contents and many other substances will produce shock on intravenous injection. Dale, Landis and Richards² showed clearly that histamine when injected intravenously produced widespread injury to capillaries throughout the body with resultant shock. With this evidence as a basis the traumatic toxemia concept of shock was brought forward by Quinby³ and Cannon and Blyss.²⁴ According to their hypothesis a toxic substance was formed in traumatized tissues. This substance was absorbed into the blood stream and was carried to distant parts of the body where it acted upon the capillaries to produce dilation and increase of permeability. Attempts to demonstrate the presence of this hypothetical toxin in the circulating blood or in blood coming from an injured area both by physiological²⁵ and by pharmacological²⁶ methods have been unsuccessful up to the present time. Underhill's²⁷ classical work on burns showed that the vessels in an injured area were more permeable in the direction of loss of plasma into the burned area but that the absorption from this area of even such diffusible substances as strychnine was prevented. The injection of blood coming from traumatized regions in Smith's²⁸ carefully controlled experiments showed that a rise in pressure generally resulted.

When the experiments which formed the basis of the toxic theory were critically analyzed by Blalock,²⁹ Parsons and Phemister³⁰ and others an alternative explanation could be found in the effect upon the circulation of the loss of blood or plasma into the traumatized area. Although it is undoubtedly correct that chemical substances from injured and inflamed areas do enter the blood stream and have their effect upon the tissues of the body, the character of the toxic reactions and the delay in their onset cast serious doubts upon their significance in the genesis of shock.

The chemical changes which take place in the body during the course of shock are brought about by the initiating factors, by the physiological reactions to the traumatic stimuli and by the failure of the circulation.

Vomiting diarrhea sweating kidney excretion and the passage of plasma into an inflamed area result in the loss of specific substances from the body. The loss of these substances results in a diminution in their concentration in the blood stream and tissue spaces unless there has been an even greater loss of water. Under any circumstance the total amount present in the body has been reduced. In shock associated with the loss of any of these substances chemical examination of the blood will reveal the corresponding discrepancy.

The elevated blood sugar which is found in shock may be regarded as one of the chemical responses of the body to trauma since it is produced by liberation of sugar from the liver through sympathetic stimulation. In shock associated with adrenal or hepatic insufficiency the blood sugar is low. The increased potassium excretion in the urine after hemorrhage may also be thought of in terms of bodily reactions to correct the disturbance since it is associated with the passage of fluid from the tissue cells into the blood stream³¹. It is recognized from the work of Zweimer and Pike³² that sympathetic stimulation liberates potassium from the affected tissues.

With progressive circulatory failure certain chemical changes take place in consequence of the tissue anoxia. These changes which are common to shock in spite of widely different initial causes have from time to time been signalized as of etiological significance in the genesis of shock. One of the first alterations to be noted was the acidosis and the consequent reduction in the carbon-dioxide content of the blood. Upon this deficit Henderson³³ postulated his respuer concept of shock. Attempts to produce shock by the injection of acid were unsuccessful and its treatment with alkali has not met with success. The acidosis present in the blood stream probably indicates only the accumulation of acids in the tissues which results from impaired oxygenation.

Zweimer and Scudder³⁴ have advanced the concept that inadequate potassium regulation is also a factor which must be considered in any explanation of shock. It seems to be established that hyperpotassemia is present in shock particularly when the condition has been brought about by widespread injury to tissues either through trauma or through anoxia. It is also probably true that an increase in the potassium of the blood is harmful to the heart and to other tissues. There is no evidence however that the hyperpotassemia itself produces an increase

in the permeability of the capillaries. Since the loss of plasma through these injured vessels is the centrally important feature of shock, it does not appear that the increased potassium in the blood is etiologically significant in the genesis of shock.

The clinical picture of Addison's disease from lack of adrenal cortical hormone is similar to that of shock. Both patients and experimental animals with corticoadrenal insufficiency⁷ are particularly liable to develop shock under traumatic conditions. These subjects are dramatically improved by administration of cortical hormone. There is no convincing proof, however, that there is a lack of cortical hormone in shock or that therapy with this hormone is effective in the prevention or treatment of this condition.

With inadequate circulation there is an accumulation of chemical substances in the tissues which possess vasodilator properties. The exact nature of these products of tissue metabolism is unknown. They produce dilatation of the blood vessels in the ischemic area (Lewis and Grant³⁷). With reestablishment of the circulation they disappear. Their concentration is determined by the metabolic rate of the tissues and the duration of the circulatory deprivation (Freeman³⁸). With prolongation of the vascular insufficiency the cells are probably damaged with elaboration of products of their breakdown. These products may be related to histamine or peptones. Their action locally appears to be both to dilate the capillaries and to increase their permeability and to them may possibly be ascribed the change in vascular permeability characteristic of shock. Our present knowledge of tissue chemistry is too inadequate to permit of more than speculation as to the nature of these substances. It seems safe to predict of future progress in our understanding of shock as in our understanding of other processes that the last word will be said by chemistry.

ETIOLOGY

Any mechanism which brings about a discrepancy between the supply of oxygenated blood and the demand of the tissues for their metabolism is etiologically significant in the production of shock. Under this principle is considered all those factors which interfere mechanically with the distribution of blood to the tissues as well as the character of the blood and the properties of those tissues to which the blood is supplied.

The most frequent cause of shock in clinical cases is a mechanical interference with the circulation of blood to the tissues. This mechanical interference comes about in five ways: (a) Insufficient volume of blood as after hemorrhage, dehydration or after major loss of plasma from burns or into an area of inflammation; (b) failure of the heart to deliver blood to the tissues as in cardiac tamponade or in cardiac failure; (c) mechanical impediment to the circulation of the blood either on the arterial or on the venous side as in massive embolism; (d) reflex disturbances in the relationship between blood volume and vascular capacity as in the fall of blood pressure in spinal anesthesia; and (e) reflex vasoconstriction which obstructs the arterial flow in the arterioles as in cold fear and pain.

(a) It is rare to encounter shock in clinical cases unless there has been serious loss of circulating plasma or blood volume. Blalock's²⁰ fundamental studies have indicated the significance of the local loss of blood and plasma into a traumatized or inflamed area. In consequence of this loss there is a reduction of cardiac output. The blood pressure is maintained by the vasoconstriction but this protective device brings about further diminution in the volume flow of blood to the tissues. He demonstrated in unanesthetized dogs that shock could be produced by graded hemorrhages provided that the circulation was impaired for a sufficient length of time.

(b) Cardiac tamponade as Cannon¹ was the first to point out provides an excellent example of shock produced by failure of the heart to deliver sufficient blood to the tissues. The arterial blood pressure may be depressed to any desired level for various periods of time. He found that after the pressure had been lowered for several hours it failed to rise even though the tamponade were relieved. The failure of the peripheral circulation in clinical cases of cardiac tamponade is well marked. So also with cardiac failure the forward failure as Harrison² has defined it there is insufficient supply of blood to the peripheral tissues with resultant shock.

(c) Mechanical impediment to the circulation of blood was used to produce shock in the experiments of Frlanger, Gesell, Gasser and Elliott.²¹ They found that shock could be caused by occlusion of the aorta below the diaphragm as well as compression of the vena cava in this location. Venous occlusion obviously impairs the return flow of blood to

the heart and in this way leads to a failure of cardiac output. On occlusion of the aorta they found, as did Welch¹⁶ that congestion occurred in the splanchnic area. There appeared to result a segregation of blood in this region. Through peripheral stagnation, the available volume of blood was reduced.

(d) Any sudden disproportion between the blood volume and the capacity of the vascular bed brought about by expansion of the latter, will result in a failure of return of blood to the right heart in sufficient quantity to maintain the cardiac output. Under these circumstances

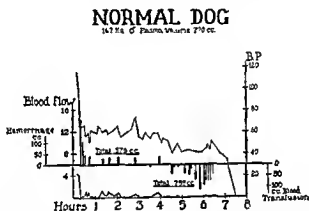


FIGURE 6. Effect of hemorrhage on blood pressure and blood flow of a normal unanesthetized dog. In this as in the following figure solid line indicates blood pressure interrupted line blood flow through the hind paw. The amount and timing of hemorrhages is indicated by solid blocks at left transfusions shaded blocks below line at right. Ordinates—blood flow and blood pressure. Abscissa—time in hours. (Freeman, Pennsylvania M. J.)

there will result a fall of blood pressure and its attendant phenomena. Spinal anesthesia according to Smith and his coworkers³⁸ produces its deleterious effects upon the circulation by diminishing the venous return through paralysis of the muscles. The syncope which attends the erect posture in the absence of muscular activity and the carotid sinus reflex disturbances may be occasioned by similar mechanisms although the possibility of reflex cardiac inhibition or reflex dilatation of the veins under these circumstances must be borne in mind. Under any condition the low blood pressure which these disturbances produce is not shock. Only when peripheral circulatory failure produces sufficient tissue anoxia to initiate progressive reduction of circulating blood volume, can the process of shock be said to have started.

(e) Vasoconstriction is a physiological mechanism which serves in a protective capacity in the face of a falling blood pressure. There is selectivity of the distribution of the reflex contraction of the arterioles with the preponderant effect in the skin and splanchnic area. In this way there is conservation of available blood flow for the vital organs, the heart and the brain in which the sympathetic control is less powerful. Freeman³⁰ has shown that this vasoconstriction, which is a protective device for the crisis, may be the ultimate cause of shock in certain conditions through the circulatory deprivation which it produces in the

SYMPATHECTOMIZED DOG

NO. 24 Q. Parav. vol. 100 cc.

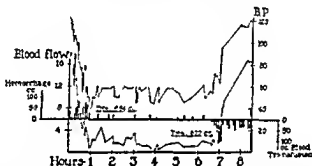


FIGURE 7. Effect of hemorrhage on blood pressure and blood flow of a dog which had recovered after bilateral thoracolumbar sympathetic ganglionectomy. At the conclusion of the experiment the dog jumped off the table and ran back to its cage (Freeman, Pennsylvania M. J.)

peripheral tissues. The dog, which has been sympathectomized by removal of both chains of paravertebral sympathetic ganglia, is more sensitive to loss of blood and will die sooner from a smaller hemorrhage than a normal dog. Yet this same animal will not go into shock, even though its blood pressure be reduced to a lower level for a longer period than in the normal dog. Figures 6 and 7 illustrate the difference in reaction between the normal and the sympathectomized dog when the blood pressure was reduced by hemorrhage. In the absence of the sympathetic nervous system the peripheral tissues are not deprived of blood to the same extent by the low blood pressure as under the influence of vasoconstriction. It is possible that certain traumatic factors, such as pain, cold and fear exert their influence in the production of shock through vasoconstriction.

The character of the blood determines its usefulness in the function of supplying oxygen to the tissues. In this manner any reduction in the oxygen carrying capacity of the arterial blood such as in anemia means that a greater volume flow of blood is necessary to meet the oxygen requirements of the tissues. Similarly if the oxygen content is reduced through inadequate oxygenation of the blood in its passage through the lungs the volume of circulation will need to be greater. Since asphyxia is capable of reflex stimulation of the vasoconstrictor mechanism the possibility of double damage to the nutrition of the body cells is present. Byliss¹⁰ has called attention to the importance of this consideration in his statement. At the risk of tiresome iteration I would again emphasize the importance of *adequate oxygen supply* to the tissues.

Another consideration which will affect the oxygenation of the cells in relation to a given blood flow is the metabolism of the tissues. In the first place the cells may be unable to use the oxygen supplied to them by the blood. Under these circumstances according to Peters and Van Slyke¹¹ a histotoxic anoxia will develop. Our knowledge of the fundamental mechanisms which determine this disturbance is too meager for discussion. An increased metabolic rate on the other hand is a well recognized condition. Fever determines an increase in the oxygen requirements of the cells to a marked extent. In this way any reduction in the available circulation will make itself felt more rapidly and with greater consequence. The *terminal shock* of acute infections and the phenomenon of a thyroid crisis are probably associated with a circulatory discrepancy engendered quite as much by extraordinary metabolic rate of the tissues as by reduction of the volume flow of blood to these cells.

PROGNOSIS

The prognosis in cases of shock is determined by the severity of the circulatory deprivation and the time during which this inadequate supply of blood to the tissues has been present. This fact is well illustrated by the rapid improvement which the patient shows in case of hemorrhage when the bleeding is stopped and a transfusion of blood is given. After shock has progressed to the stage of hemoconcentration with segregation of the blood in the peripheral and splanchnic capillaries no therapy can interrupt the vicious circle. The time factor in shock has been forcibly stressed by Cannon.¹

TREATMENT

Since shock is the progressive loss of circulating blood volume due to the tissue anoxia which results from impaired circulation it is imperative to interrupt the process at the earliest possible moment before serious tissue damage is produced. In order to check the course of shock an adequate supply of oxygenated blood sufficient to meet the tissue requirements must be achieved. The etiological factors have been enumerated above and the treatment of shock will be described under the same categories.

(a) Since shock is usually produced by insufficient volume of blood or plasma replacement of this loss is the most effective therapeutic agent. In case shock has been brought on by hemorrhage transfusion of blood is manifestly the appropriate treatment. The lost blood should be replaced at the earliest possible moment after the bleeding has stopped. There are two circumstances which may prevent the carrying out of this objective. Lack of suitable blood and in a condition when further bleeding is to be feared.

In default of appropriately matched blood there are various blood substitutes which may be used. Fresh plasma is probably the best of these substances.⁴² It will provide the necessary volume with a colloid osmotic pressure which will hold it in the vascular system. It lacks the oxygen carrying capacity but the hemoglobin content of the blood can be reduced to extremely low levels without great harm provided that the volume be maintained. The possibility of the storage of plasma in the dried or lyophile form offers opportunities for wider usefulness.⁴³

Gum acacia was suggested as a blood substitute by Bayliss.⁴⁰ It has approximately the same viscosity in a six per cent solution that plasma has and has the advantage over solutions of electrolytes that it exerts a colloid osmotic pressure. It is held within the blood stream for long periods of time. The drawback to the use of acacia is the difficulty of its elimination. Traces have been found in the circulation as long as three years after its administration.⁴⁴ Its deposition in the liver has been noted. In an emergency it is valuable. Five hundred cubic centimeters of a six per cent solution are given intravenously with immediate benefit in restoration of blood volume.

The circulatory volume can be temporarily sustained by the intravenous administration of physiological saline or five per cent glucose.

This fluid is held in the circulation for as long as an hour and should be used in the treatment of hemorrhage until blood or some better substitute becomes available. In cases of hemorrhage which are not serious the body will be able to make its own readjustment provided that sufficient water and salt can be called on.

In the treatment of hemorrhage fluids administered by the gastrointestinal tract seem to be better handled than fluids administered parenterally as Robertson and Bock³ showed. In many cases vomiting or gastrointestinal hemorrhage will prevent the intake of fluids by mouth. In such cases water or salt solution can be given by rectum.

The fear is occasionally expressed of giving fluids intravenously because of the danger of overloading the circulation. For this reason their administration by hypodermoclysis has been advocated. The danger is probably overestimated as the quantitative studies of Altschule and Gilligan⁴² have shown. The normal circulation can tolerate the intravenous administration of isotonic fluid at a rate of 10 to 20 cc per minute without any rise in venous pressure. In cases of congestive heart failure with increased venous pressure fluids can be given slowly at 2 to 1 cc per minute without increasing the pressure since the salt solution leaves the circulation at approximately the same rate. The disappearance of fluid from the subcutaneous spaces when injected hypodermically is probably more rapid than the slow rate at which it is given intravenously by the drip method now employed. An additional reason for giving it into the vein is the freedom from discomfort.

In case that further bleeding is to be feared the treatment of hemorrhage offers one of the most difficult problems in judgment which the practice of medicine affords. The ideal to be striven for if surgical intervention is not feasible is the maintenance of life until the physiological and chemical forces of the body should have controlled the bleeding. In the final analysis the patient should be allowed to go to the edge of shock without entering the vicious circle of progressive loss of circulating blood volume through tissue anoxia. With this concept in mind upon what considerations can the physician depend to guide him in his treatment? Here as in few other conditions the most careful watch should be kept for signs of oncoming shock. One of the earliest evidences that the body is under strain is restlessness. In experiments on dogs under local anesthesia¹⁸ it was repeatedly observed that restlessness was a pre-

monitory sign of shock. This change in the behavior seemed to occur at a critical period when the additional loss of a small amount of blood would precipitate the downward course.

A rising pulse rate and a falling blood pressure are unmistakable signs of shock. They may not give such specific indications of the correct time to take measures to prevent shock as the behavior of the peripheral circulation. As long as there appears to be an adequate supply of blood to the periphery as indicated by a pulse of palpable volume and warm extremities shock in the presence of hemorrhage, need not be feared. The appearance of the lips, the ears, the nose and the circumoral region is of diagnostic significance. When vasoconstriction produces an ashen appearance and the face and hands are cold and sweaty, the process has reached a crisis which demands intervention. Frequent determinations of the concentration of the blood should be made. As long as dilution is proceeding after hemorrhage the process is one of restoration of blood volume from the extravascular fluid reservoirs. When the process of dilution is checked or if concentration occurs the process of shock has then already started.

The treatment which seems to offer the best results in maintaining life in the face of continued bleeding is the continuous drip transfusion suggested by Marriott.⁴⁰ During the course of this treatment careful observation of the general condition of the patient must be made.

The administration of stimulating drugs in shock from hemorrhage is not only useless but probably harmful except as a last resort if a fatal outcome seems imminent.

In shock brought on by dehydration treatment demands first of all the replacement of the fluid lost. In this restoration it is of importance to appreciate the fact that various salts have been lost in addition to water when dehydration has been caused by excessive vomiting, diarrhea, drainage or urinary secretion. It is essential also to realize that through insensible perspiration there has been going on a loss of water without salt. It is hard to say which of these losses it is the more imperative to replace. From the standpoint of mechanical volume the administration of water is the chief factor. The electrolyte balance, however, must be maintained in order to permit proper functioning of renal and other tissues. Fortunately in the form of 0.9 per cent sodium chloride solution (physiological saline) both salt and water are available. Provided that the

kidneys are able to function the body can regulate the excretion of either anions or cations so as to achieve the necessary balance.⁴⁷ However a supply of water is essential for adequate renal function. Five per cent glucose in distilled water is more readily excreted than physiological saline. The total quantity of fluid necessary to correct a state of dehydration is large. Maddock and Collier⁴⁸ have determined the fluid needs in surgical patients and have found that it was necessary to give as much as six per cent of the body weight in addition to the daily requirements to correct the state of dehydration present in patients at the time of admission. Collier and his associates⁴⁹ have described the technic for replacement of the salt lost by vomiting, diarrhea and profuse drainage.

Even though the external loss has been one of water and salts alone when dehydration reaches a critical stage of impending shock recovery will not always follow replacement of the lost materials. Keith⁵⁰ in his experiments upon dehydration produced by the intravenous injection of sucrose found that if the state of dehydration were not allowed to persist for long recovery by replacement was effected. However if he waited too long before replacing the fluid lost recovery could not be brought about.⁵¹ The clinical experience of pediatricians in dealing with dehydration associated with diarrhea and vomiting showed that in the serious cases the fluid administered was not retained in the circulation but was found at necropsy in the tissue spaces and in the serous cavities. It seems probable that the decreased circulation brought about through dehydration produces sufficient tissue anoxia to impair the permeability of the vessels so that a loss of plasma ensues with consequent reduction of total amount of plasma protein in the circulation. Even though the concentration of plasma proteins is elevated during the course of dehydration the absolute amount is decreased. Support for this concept is furnished by the consistency with which low values for the serum protein concentration are found after recovery from dehydration has been effected. This reduction in the serum protein concentration facilitates the development of edema particularly in the presence of excessive administration of salts. Thompson, Raydin and Frank⁵² have emphasized the significance of low blood proteins in faulty postoperative wound healing. Hypoproteinemia is. Boden, Raydin and Fricker⁵³ first showed disturbs the function of the gastrointestinal tract.

The following case illustrates the treatment by transfusion of a patient suffering from shock as a result of dehydration

CASE 1 F. P. Del University Hospital No 37 122 The patient was a white man of 36 years who had sustained four previous abdominal operations for regional ileitis. He was first admitted to the hospital 18 hours after the onset of acute intestinal obstruction. There was distention and fecal vomiting. He was in *extremis* with a systolic pressure of 60 and a pulse rate of 134. His extremities were cold and cyanotic. There was marked tetany with positive Chvostek sign. The blood studies showed a red cell count of 4.76 million and a hemoglobin of 90 per cent. The white blood cells numbered 8300. The chlorides were 83 milli-equivalents per liter and the carbon dioxide capacity 36 volumes per cent. Immediate intravenous treatment was started. In the succeeding 18 hours he received 1150 cc of blood and 1130 cc of five per cent dextrose in physiological salt solution. The stomach was decompressed by suction through a Miller Abbott tube. At the end of 18 hours the clinical picture had changed dramatically. The pulse was 92 with full volume and the extremities warm and dry. Blood studies repeated the following day showed that the chlorides had come up to normal 102.8 milli-equivalents and the carbon dioxide to 62 volumes per cent. The serum proteins were 4.8 grams per 100 cc in spite of the fact that he had received 1920 cc of blood in multiple transfusions. The hemoglobin did not exceed 96 per cent although the red blood count on the second day went up to 5.01 million. This patient illustrates the necessity of administering fluid with colloid osmotic pressure which will stay in the circulation. The low serum protein concentration even after giving so much blood indicated the severity of total circulating protein deficit that must have existed at the time of admission.

Through exudation of serum from a burned area or by the loss of plasma into an area of inflammation the circulating plasma volume is frequently reduced. This loss is always a serious one since in addition to the decrease in blood volume there is hemoconcentration with increase in the blood viscosity which leads to further impairment of circulation. Replacement of the lost fluid by the intravenous injection of fluids without colloid osmotic pressure will not restore the plasma volume. The vessels are unable to retain the fluid injected and the concentration of the blood is not relieved. Treatment by transfusion is effective through increasing the blood volume but here, as in few other conditions, the optimum therapy is the administration of plasma⁴. Not only is the volume of the circulation increased but the condition of hemoconcentra-

tion is relieved. In shock from acute pancreatitis or from strangulation of the intestine the loss of plasma into the peritoneal cavity is large. The fluid has a protein content which ranges from two to four per cent. Treatment demands the replacement of the protein as the following case illustrates.

CASE 2 D S University Hospital No 38 182 The patient was a 16 year old girl with ulcerative colitis of three months duration. She was acutely ill on admission quite pale and washed out. The abdomen was doughy and tender along the course of the colon. The red blood count was 4.1 million and the hemoglobin 74 per cent and the white blood count 14 000. By the following day the hemoglobin had fallen to 68 per cent in spite of a transfusion of 500 cc of blood. A note was made that the patient shows marked hyperactivity of the sympathetic nervous system chiefly characterized by peripheral vasoconstriction on afferent stimulation. The diarrhea continued with between 7 and 11 loose stools each day. These bowel movements contained blood and pus. In the next three days although she received four transfusions in which a total of 1400 cc of blood were given the red blood count dropped to 3.58 million and the hemoglobin to 62 per cent. An ileostomy was then performed. Upon opening the peritoneal cavity a large amount of free fluid was encountered. This fluid on analysis proved to have a protein content of 3.2 grams per 100 cc. The bowel wall was inflamed but was not covered with fibrin. Culture of the fluid yielded no growth of bacteria. After operation she received three blood transfusions and the hemoglobin came up to 96 per cent.

This case is presented to illustrate the large amount of blood which is lost from the inflamed gastrointestinal tract. Further loss of plasma into the peritoneal cavity even without frank peritonitis brings about additional reduction of circulating blood volume. Treatment by the injection of water and salts alone will not replace the osmotically active substance which has been lost with the plasma.

(b) When the peripheral circulatory failure has been brought about by failure of the heart to deliver an adequate supply of blood to the tissues therapy must be directed toward improving the cardiac function. Specific treatment of the failing heart has been taken up in Chapter XXXIV.

The process of shock will occasionally be encountered in a patient who has a damaged heart and the question will come up as to whether or not the circulation will stand the administration of blood plasma or other intravenous fluid. In answer to this question it is only necessary to

emphasize the fact that the myocardium needs an adequate supply of blood for its proper functioning. Correction of a low blood pressure and of hemoconcentration will probably result in an improvement of cardiac function. Again cardiac hyperactivity is one of the most fundamental physiological reactions to shock. When the crisis is passed the stimulation subsides. From these considerations the conclusion is reached that shock should be treated in the cardiac patient from the standpoint of the heart if that organ is the primary factor. Otherwise therapy should be directed toward relieving the burden which alteration in the state of the circulating blood volume places upon the heart.

(c) Where shock is brought about through gross obstruction of the arterial or venous circulation best results will naturally follow removal of the obstruction. In only occasional instances will this solution be possible. The development of collateral circulation is effective provided that time is allowed but with sudden obstruction as by an embolus a condition develops which frequently goes on to shock and death before the collaterals can develop. The original obstruction may not alone be sufficient to produce death but there develops from that block an extensive thrombosis which precludes recovery. If the arterization thrombosis can be prevented time is allowed for the development of collateral circulation.

Heparin^{7,8} has recently been developed for intravenous use in patients. It will prevent the extension of the thrombotic process. In addition the development of further emboli is prevented. The solution is supplied by the Connaught Laboratories of Toronto. It should be given by the continuous intravenous drip. The contents of two vials or 20,000 units daily will increase the clotting time from 7 to somewhere between 15 and 18 minutes. In a series of six cases of sublethal pulmonary embolism there were no deaths and no recurrence of the embolic phenomena. In peripheral arterial embolism the prospect of successful surgical removal is increased by the administration of heparin since thrombosis at the suture line is inhibited. Even in case that the removal cannot be accomplished arterization thrombosis is prevented so that there is time for the reestablishment of the circulation through collaterals. Mesenteric thrombosis has also been treated with consistent success by the use of this material. Heparin is thus of use in the treatment of

shock when there exists a mechanical obstruction to the flow of blood from a clot in the vessels

(d) The only occasion when stimulants are effective in the treatment of shock is when the process is being initiated through the fall of blood pressure which results from reflex inhibition of cardiovascular or muscle tone. Even in these circumstances the preventive treatment by administration of the drug before the fall is more effective than after the fall in blood pressure has occurred. Henderson⁵⁶ and his coworkers have shown that a decrease in muscle tone may occur in patients after operation and that this drop is prevented by the use of strychnine. A current of air played upon the skin is also effective in restoration of tone. He and his associates⁵⁷ found that the weakness experienced by an individual in a humid environment without movement of air currents was associated with low muscle tone and that this condition could be corrected by keeping the air in motion. It is possible that the beneficial effect of adequate ventilation is due to the increase in tone produced in this way.

The time honored use of the recumbent posture is the most effective method of improving the circulation when the depression results from pooling of blood in the venous reservoirs. The head-down position favors the return of blood to the right heart. After spinal anesthesia has been induced, a serious fall in blood pressure and syncope will be produced if the body is raised into the vertical position. In the prevention of the fall in blood pressure under spinal anesthesia, the use of vasoconstrictor drugs seems to have a logical place which has been confirmed by experience. Ephedrine in doses of 25 mg. a half hour before injection of the anesthetic and, in case that the pressure is not elevated, immediately before the solution is injected into the subarachnoid space, is usually effective in preventing a serious fall in blood pressure.⁵⁸ After the spinal anesthesia has been administered, this drug is not so effective in restoring a pressure which has fallen. The use of adrenalin, benzedrine, and neo-synephrine has been found valuable under these circumstances.

Recent investigations by Kunkel, Stead and Weiss⁵⁹ have shown that in piredrinol, there is afforded a substance which increases the venous tone without at the same time producing marked vasoconstriction in the arterioles. It was effective in preventing syncope induced by the administration of nitrites when the subject was tilted in the horizontal position.

Its use in the treatment of clinical shock on the medical wards especially if there was a decrease in blood volume was not beneficial.

There are various other methods of increasing muscle tone in order to raise the venous pressure. An interesting one was recently suggested by Ornstein, Licht and Herman.⁶⁰ They stimulated the muscles of the abdomen and buttocks with faradic current and observed an increase in venous pressure. Its successful use in the treatment of traumatic shock was reported in one case. This method would appear to be too cumbersome for general use. A simpler method and one which was used for

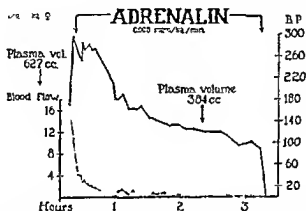


FIGURE 8 Effect of intravenous injection of adrenalin (0.003 mg per kg per minute) on blood pressure, plasma volume and blood flow through the hind paw of an unanesthetized dog. Solid line—blood pressure. Interrupted line—blood flow. Arrows indicate plasma volume measured by the blue dye T-1824 at times indicated. Ordinates—blood flow left and blood pressure right. Abscissa—time in hours. The blood flow is recorded in cubic centimeters per 100 cc tissue volume per minute (Freeman, Pennsylvania M. J.).

many years is centripetal massage of the extremities. It seems likely that blood which is stagnant in the peripheral portions of the body may be brought back into the circulation by this method. Provided that the blood flow to the tissues of the body is not too long impaired the process of shock will not be initiated.

(c) Vasoconstriction is one of the protective mechanisms of the body which is brought into play by trauma or the expectation of injury. It is useful in the emergency, to mobilize the resources of the organism. The physiological attributes of vasoconstriction have been discussed in the section of this chapter devoted to the consideration of the physiology of shock. Even though constriction of the vessels of the peripheral portions of the body is beneficial in the crisis serious consequences are pro-

duced if that constriction is too protracted. The arterioles are contracted and although the pressure proximal to the narrowing may be raised blood flow is reduced. The nutrient supply to the tissues may be so far cut down that actual necrosis may ensue. Such an event is to be seen in the gangrene of the finger tips brought about through frequent spasms of the digital arterioles in Raynaud's disease.

Generalized vasoconstriction such as that which results from the intravenous administration of adrenalin may be so intense and produce such a deficiency in the blood supply to the tissues that shock can be produced. In the unanesthetized dog as shown in Fig. 8 if the dosage of adrenalin is increased to produce a severe reduction in peripheral blood flow a marked decrease in blood volume with hemoconcentration results.³⁰ On microscopic examination of the tissues there is found congestion in the minute vessels of the splanchnic area.

The vasoconstriction hypothesis is useful in that it provides an explanation of the fact long recognized that pain, fear and cold are capable of producing shock or of aggravating the condition if present. The fundamental physiological reaction of the body to these stimuli is vasoconstriction. It is a purposeful response. If the emergency is too severe or protracted the very mechanism by which the body strives to survive may bring about its ultimate dissolution. *Clinical cases of shock precipitated by fear have been encountered and a surgeon of such wide experience as J. M. T. Finney³¹ has emphasized the importance of the emotional attitude of the patient prior to operation. The following case history is given to illustrate the physiological reaction produced by apprehension in a patient.*

CASE 3. G. H. Massachusetts General Hospital No. 349187. The patient was a 43-year-old white female who was operated upon for uterine bleeding. A total hysterectomy was performed under ether and local anesthesia. Before operation the patient had been examined by four different physicians and they had all commented upon the emotional instability which she manifested. During the course of her operation although the blood pressure was well maintained the pulse rate was 112 beats per minute. Special care was taken to prevent the loss of blood and after operation she was given 1800 cc. of fluid intravenously. That night her condition was excellent pulse 92, blood pressure 100/80. However she was sweating and uncommunicative. The following morning she was in shock with a pulse of 150 and a blood pressure of 91/86. Her

skin was cold and clammy. She was vomiting coffee ground material. Examination failed to reveal intraperitoneal hemorrhage or other cause for her condition. It was felt that she was suffering from shock brought about through fear. She was transferred into a separate room and studies of the volume flow of blood through her hand were made. At the start the flow was very low. During the course of the examination which lasted for one and one half hours no attention was paid to her condition. No treatment was instituted. As the studies were calmly pursued a steady increase in the circulation through her hand was observed. At the end of the time the flow was normal. She opened her eyes and the skin of her face became flushed. The extremities were warm and the pulse of good quality. She proceeded in a normal convalescence. This case is presented to illustrate the profound physiological effects which can be brought about through emotional distress.

One word of caution is needed in the interpretation of so called psychic shock. The diagnosis can be suspected but not until adequate organic cause for the condition is excluded either by recovery or by careful necropsy can the nature of the etiological factor be established.

In the treatment of shock produced or aggravated by vasoconstriction it is necessary to inhibit the action of the sympathetic nervous system. To produce this inhibition either the exciting cause can be eliminated or the patient prevented from reacting to the stimulus. It might be considered advisable at first glance to block the sympathetics on the efferent side since it was shown that the sympathectomized animal will not go into shock. However even though this animal will not go into shock it will succumb from hemorrhage more readily than the normal animal since it cannot maintain through constriction of the vessels a blood pressure sufficient to supply blood to the brain. If the patient were deprived of his sympathetic nervous system he might not be able to respond to the crisis at all. Although shock would not be produced the patient would die. From this consideration it would seem more logical to inhibit the sympathetic system by removing the stimuli which call it into activity. The treatment of shock should be based on the causes of vasoconstriction as enumerated in Fig. 9.

When pain, fear and cold are producing vasoconstriction the obviously correct therapy is morphine, reassurance and warmth. These remedies are the classical ones in the treatment of shock and assume new significance in view of the vasoconstrictor hypothesis. For other fac-

tors which stimulate the sympathetic nervous system such as dehydration and hemorrhage the treatment has been detailed above and again is well established

When the patient is gripped by fear it may not be possible to reason with him or reassure him. It is in this instance that the administration of alcohol intravenously as Frazier¹² suggested has a definite place. It can be given by continuous venoclysis 30 cc (1 ounce) to 500 cubic centimeters (1 pint) of five per cent glucose or salt solution. The patient is kept pleasantly inebriated and is indifferent to his surroundings. At the same time the alcohol produced peripheral vasodilatation and offers a supply of readily combustible carbohydrate.

SHOCK

<u>CAUSE</u>	<u>TREATMENT</u>
Hemorrhage	→ Transfusion
Dehydration	→ Fluids
Pain	→ Morphine
Cold	→ Warmth
Fear	→ Reassurance
Asphyxia	→ Oxygen
Exhaustion	→ Rest

FIGURE 9 The treatment of shock (Freeman, Pennsylvania M. J.)

The therapy of shock aggravated by deficiency in oxygen carrying capacity of the blood is clearly the restoration of the hemoglobin content by transfusion. In case that the oxygen content is reduced by asphyxia the administration of oxygen by inhalation is valuable. In some clinics the routine treatment of shock embodies the use of oxygen at high tension. When the oxygen saturation of the arterial blood is already normal the use of oxygen does not seem to rest on a rational basis. Its use in shock from asphyxia is imperative.

When there is reduced peripheral blood flow combined with an increased rate of utilization of oxygen by the tissues as in fever or in hyperthyroid states a condition of tissue anoxia is more readily brought about. In addition to therapy directed toward increasing the supply of blood to the tissues efforts should be directed toward reducing the tissue needs by lowering the metabolic demands. The temperature must be

kept from reaching excessive heights. To this end ice bags, exposure of the body to cool air and ice packs may be used. Frequently, especially in states associated with extreme vasoconstriction the extremities will be cold while the body is raging with heat. Under such circumstances ice water enemata may be employed.

In shock associated with toxemia from infections, specific therapy with antitoxins is useful where possible. Again surgical drainage of infected collections frequently bring gratifying results as far as the general condition is concerned.

CONCLUSIONS

Shock is the clinical condition characterized by progressive reduction of circulating blood volume brought about by tissue anoxia which results from inadequate circulation.

The clinical picture depends upon the physiological reactions to the traumatic stimuli and upon the bodily responses to inadequate circulation.

The pathological findings are those of stagnation of blood in the peripheral and splanchnic areas and of tissue damage from inadequate circulation.

The most significant physiological alterations are those of the cardiovascular system and they give evidence of widespread sympathetic stimulation.

The chemical changes are chiefly dependent upon the circulatory deficiency. No chemical substance capable of producing shock has yet been consistently demonstrated in the circulating blood in sufficient quantity to cause shock.

Any mechanism which brings about a discrepancy between the supply of oxygenated blood and the demand of the tissues for their metabolism is etiologically significant in the production of shock.

Duration of circulatory impairment determines the prognosis.

Treatment should be directed toward assuring an adequate supply of oxygenated blood to the tissues. Only when this aim has been achieved can the therapy of shock be termed satisfactory.

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CHAPTER XLVII

HYPERTENSIVE ARTERIAL DISEASE

By EDWARD J. STIEGLITZ, M.D.

Introduction Preventive medicine has greatly advanced the life expectancy of man. In the last 40 years the average life expectancy at birth has increased 17 years from 48 years in 1900 to 65 years today. Consequently the illnesses and disturbances of middle and late life are constantly increasing in significance and frequency. Arterial hypertension or more properly hypertensive arterial disease is one of these. Though not limited to the later years of life, hypertensive disease is most often observed after 45 years of age. Today there are more elderly people than there ever were before and in the future the ratio of old to young will become progressively greater. Geriatrics and the degenerative diseases are of far more than mere academic interest today; these problems clamor for prompt and vigorous attention.

Hypertensive disease is insidious and asymptomatic for a long time as it advances to inevitable injury. This lack of early symptoms is one of the greatest obstacles to conquest of the menace. As with cancer, arteriosclerosis, chronic nephritis, coronary disease, diabetes and the degenerative disorders in general, there must be clinical search for the disease if we are to discover crises early enough to accomplish much in curtailing the rising mortality and invalidism. To wait for subjective symptoms to appear is but to invite disaster for many. Truth, whether in diagnosis, research or ethics, is a mistress demanding constant pursuit.

Incidence It is difficult to evaluate the incidence of hypertensive disease. That it is large and distinctly increasing is unquestionable. Summarization of numerous statistical inquiries place the frequency of hypertension in the neighborhood of eight to ten per cent of all American males under age 45, with increasing figures rising to nearly 30 per cent around age 60. In women the incidence is slightly less up to the time of the climacteric, after that the incidence is equal or greater than that in

men Of these hundreds of thousands of hypertensive individuals only a relatively small number have knowledge of their hypertension

Mortality and Causes of Death The mortality of hypertensive arterial disease is likewise an uncertain numerical figure This may be attributed largely to the fact that hypertensive disease contributes to several different causes of death Conservative estimates place the annual deaths from hypertensive disease in the United States above 150,000 Carefully compiled mortality statistics from the large life insurance companies indicate that the mortality rate is doubled or trebled over the expected normal death rate when hypertension is the sole cause for rejection Although numerous persons survive for many years—hypertensive disease is very slowly progressive—the average life expectancy is greatly shortened thereby This does not imply that every hypertensive patient is in acute and dire jeopardy for early in the course of this insidious disease there is little immediate risk The progression of the disorder is usually slow and gradual but dreadfully persistent There is no evidence whatever that hypertensive disease once fully established tends to regress or be self-limited Many years may elapse between the onset and the final but inevitable termination Early discovery with the institution of prophylactic measures may prolong this interval and postpone the ultimate invalidism and disability

The major causes of death in hypertensive arterial disease are cardiac exhaustion or defeat, cerebral hemorrhage, pneumonia and renal decompensation occurring in the frequency of the order named Cardiac exhaustion from the ever-increasing burden of the rising peripheral resistance accounts for somewhat more than half of the deaths¹ The relationships of cardiac failure to hypertensive disease are discussed in Chapter XXXV

Disability Disability ranging from minor infringements upon permissible activities to the complete helpless invalidism of the apoplectic or cardiac cripple is an even greater cause for concern than the mortality from hypertensive arterial disease The life span of man is after all limited by definite biologic phenomena of senescence Preventive medicine has its limitations But if we may reasonably control degenerative disorders so that the prime of life be prolonged and premature disability largely avoided until senility really equals infirmity then geriatrics will have contributed immeasurably to the welfare of mankind The greatest

disability and invalidism from hypertensive disease occurs in the late forties and the fifties when productivity and usefulness should be at their peak. With more than half of the deaths from hypertensive disease due to cardiac failure manifested either as congestive decompensation, coronary occlusion or aneurysm pectoris it is not hard to visualize how truly tremendous is the total disability from this disease. About one fifth of the deaths result from cerebral apoplexy and many more patients have nonfatal but disabling strokes.

Symptoms The tragedy of hypertensive disease is accentuated by its insidiousness and by the fact that it so often attacks those whose energy, productive imagination and fine sense of responsibility make them most valued members of the community. Though not sharply limited to any one physical or mental type of person, hypertension does exhibit a predilection for the doers rather than for the drones.

The absence of subjective distress of any sort in the early stages of hypertensive disease is the greatest barrier to effective control. Many of these individuals have in unusual vigor and enthusiasm and are totally unaware of their early hypertension. The majority of instances of early hypertension are first discovered rather coincidentally upon examination for some other purpose. It can not be overemphasized that inclusion of blood pressure determinations should be an integral and invariable part of every physical examination. This applies not only to examinations of patients in the fourth to sixth decades of life but to those of all ages and with all complaints. In children and young adults hypertension may be a sequel to acute infections with or without nephritis. Hypertension in pregnancy is very dangerous. It is certainly more important to discover early hypertensive arterial disease in a young woman before she becomes pregnant rather than after gestation has commenced and the problem is greatly complicated. Routine preoperative determination of the arterial tension may forewarn of hazardous risks.

It is true that in the last several years there has arisen an increasing public consciousness of the importance of silent hypertension. It is upon the general practitioner that the responsibility for early diagnosis rests. It is through him that the general public should receive most of its accurate and valuable information. It is he who has the greatest opportunity for frequent examination and who is in the best position to anticipate

difficulty because of his intimate knowledge of the family history, environmental background and personality of his patients.

Diagnosis The diagnosis of hypertension or hypotension is one of the simplest problems of clinical medicine and yet one of the most difficult. It is only necessary to determine the blood pressure to discover the *presence* of such abnormality. But the discovery of the existence of hypertension does not suffice. Diagnosis to be complete and fully useful must include far more than this. Consideration of the etiologic factors, the extent of permanent irreparable anatomic injury, the degree of cardiac and renal functional reserve and the existence of complications must all be included in a truly comprehensive diagnosis. Effective therapy must be based upon etiology. In hypertensive disease this is extremely complex and variable. Thus the wisest therapy is inevitably highly individualistic.

It is important that the determination of the arterial tension be done correctly (see Chapter XLIII) and that careful consideration be given to the various factors which may cause transient variations in the tension. Upon one occasion at least the tension should be observed in *both* arms. Asymmetry of the tension is far more frequent than is commonly appreciated and it is sometimes of considerable magnitude. In one series of some 600 consecutive examinations² clinically significant differences in the blood pressure of the two arms was found in some 16 per cent. In those patients with hypertension this frequency was increased to 27 per cent. There are many instances where failure to make a bilateral determination of the blood pressure results in gross and grievous diagnostic error. The reasons for such asymmetry may be obscure, but often there are significant and serious lesions such as some intrathoracic mass (aneurysm or neoplasm), aortitis, cervical rib or cerebral lesion with trophic disturbance.

CASE EXAMPLE Mrs. R. L., aged 43, a surgeon's wife, had for several years complained of discomfort in the region of the left shoulder, left anterior axillary line and down the left arm. This discomfort was described as a numb pulling sensation. The existence of actual pain was denied. The patient admitted that were it not for her constant fear of a mammary cancer (her mother and one maternal aunt had died of cancer of the breast) she could train herself to ignore the distress. But with this fear the discomfort was becoming increasingly annoying, particularly as examinations by several physicians had failed to reveal any

explanation thereof. There were no demonstrable foci of infection. The cardiac and pulmonary findings were entirely normal. No lesions of the breast could be detected. Asymmetry of the arterial tension was discovered, however. The pressure was 110/70 on the right and 94/60 on the left. This degree of asymmetry persisted on repeated examinations. An antero-posterior x-ray film of the base of the neck was obtained on the immediate suspicion that a cervical rib accounted for both the subjective and objective symptoms. The film confirmed these suspicions and although surgical intervention was *not* advised, the relief of definitely knowing the cause of her paresthesia gave her great comfort.

CASE EXAMPLE. Mr. H. S., aged 31 indignantly requested expert explanation of why one life insurance company flatly rejected him as a risk because of hypertension whereas but a month previously his application for a large policy had been accepted by another company at standard rates. He felt perfectly well. Bilateral determination of his arterial tension revealed a severe asymmetry. Right 190/120 left 118/76. Careful questioning elicited the information that the two different medical examiners had measured his blood pressure on different arms. Auscultation of his heart yielded normal findings but fluoroscopic and film x-ray examination of his chest revealed a small but distinct aneurysmal sac upon the aorta at a point where it could well interfere with the circulation to the left upper extremity. His Wassermann reaction was strongly positive. The patient soon realized his luck in obtaining the one insurance policy and the insuring company began to take an interest in the desirability of *bilateral blood pressure measurements*.

PATHOLOGIC PHYSIOLOGY

An understanding of the circulatory mechanisms, the factors which control the arterial tension and which maintain circulatory equilibrium are necessary to the intelligent interpretation of abnormal findings. The observation that the blood pressure is elevated does not alone justify the conclusion that hypertensive disease exists. Hypertension or hypotension are *physiologic states* like fever or edema and *not* diseases. Either is but an exaggeration of a perfectly normal and vital physiologic phenomenon for an *intrarterial tension* is *absolutely necessary* for the maintenance of the circulation and thus of life. No new mechanisms are involved in such deviations from the normal. There is not nor can there be a sharp line of distinction between purely physiologic fluctuations and pathologic changes. The most satisfactory and definitive term for the characteristic disease in which hypertension is the chief clinical phenomenon is *hypertensive arterial disease*. The term *arterial hyper*

tension denotes the state of elevated blood pressure. The popular term essential hypertension is misleading in that essential means idiopathic or without cause and hypertension is anything else never arises without cause. Just because the etiology is obscure and difficult of appraisal is no justification for denying the existence of cause. Hypertensive disease though it expresses itself in manifold symptoms and consequences has distinct biologic unity and a consistent pathogenesis. All the sequelae and consequences are attributable to the impairment of tissue nutrition and oxygenation due to arteriolar constriction. The equilibratory mechanisms of the circulation are delicate and complex. It is through disturbance of this equilibratory mechanism that hypertension and later hypertensive disease arise.

The maintenance of the circulation is primarily dependent upon the propulsive effect of the contracting heart. Any failure of the heart from whatever cause inevitably results in circulatory failure. The work involved is tremendous. The human adult heart moves from 5 to 10 liters (11 to 22 pounds) of blood per minute or 125 to 200 cc per beat. Thus about ten tons of blood are moved per day. This represents merely the weight of the blood moved and does not take into consideration the resistance to such motion e. g. the diastolic tension.

Peripheral Resistance. In opposition to the propulsive activity of the heart is the peripheral resistance of the vascular tree and the inertia of the blood. Alterations in the arterial tension are reflections of changes in the peripheral resistance and the efforts of the heart to overcome these. The diastolic tension essentially represents the peripheral resistance; the systolic tension equals this plus the cardiac force at systole. As the diastolic tension rises so must the systolic tension if circulation is to be maintained. The cardiac burden is greatly increased by any rise in the peripheral resistance.

The peripheral resistance to the circulation is dependent upon a number of factors. These factors are of varying importance and they are not all subject to the same degree of physiologic or pathologic fluctuation. One factor is the viscosity of the blood. This is relatively constant. The viscosity is chiefly dependent upon the cell count for the viscosity of the plasma is relatively low. Changes in viscosity are of significance to the mechanics of the circulation only when the cell counts exceed 5,000,000 erythroplastids per cubic millimeter. The increase in peripheral resist-

ance due to elevated viscosity affects chiefly the capillary circulation which has a very minor effect upon the arterial tension as a whole.

The most important and variable factor controlling the peripheral resistance is the resistance of the arterial walls to stretching. The degree of arteriolar constriction. In common with all blood vessels these structures act as (1) conduction ducts, they also control the (2) distribution of the blood to various parts of the body by appropriate relaxation or constriction in areas of increased or diminished work respectively, and they (3) act as a dam with sluice gates to control the head of pressure in the circulatory system proximal to the arterioles. The walls of these smaller arteries consist chiefly of spirally arranged smooth muscle fibers, under the direct control of the sympathetic nervous system.

As blood flows onward from the aorta and into the larger arteries and then into the smaller and smaller branches, the diameters of the individual vessels gradually become less but the total area of the vascular bed becomes larger. The intravascular tension falls. This fall is but slight up to the level of the arterioles, from 50 to 60 per cent of the reduction in pressure from aortic to venous levels occurs in the arterioles. Thus the degree of constriction, or *verage tonus*, of the *last numbers* of small arteries and precapillary arterioles is responsible for a large fraction of the peripheral resistance. This is indirectly reflected as the diastolic tension. Constriction or relaxation is dependent upon the constant flow of impulses along the sympathetic nerve fibers to the smooth muscle of the arteriolar walls. Fluctuations in the intensity of these stimuli or in the excitability of the musculature control the vascular tone and in turn the diastolic tension. The vasomotor nerves are derived from the anterior spinal roots from the first thoracic to the fourth lumbar segment. *The vessels of the head, neck and extremities are innervated by fibers from the spinal cord*, but the whole apparatus is controlled to some degree by a medullary center both through the cord and the vagus nerve. There may be reflex reactions through the sympathetic system without apparent cord connections.

Most changes in arteriolar caliber are not reflected in the systemic arterial tension because they are of a local nature and are compensated for by localized constriction or relaxation elsewhere. The whole circulatory tree is in a constant state of flux and adjustment to maintain a relatively constant equilibrium and *only* generalized changes of consider

able magnitude are clinically discernible. For example, during the period of postprandial digestion there is splanchnic vasodilation and a compensatory peripheral (cutaneous) and cerebral vasoconstriction. This accounts for the typical after dinner somnolence and the greater ease with which we are chilled during digestion. It is significant in considering the splanchnic peripheral reflex balance to remember that the renal circulation is effected as that of the skin. Thus factors which cause peripheral vasoconstriction such as chilling likewise cause renal vasoconstriction and ischemia while the splanchnic area is in a state of active hyperemia. This phenomenon is probably partially responsible for the tendency to renal injury following peripheral chilling.

Control of Arteriolar Tone This whole equilibratory or homeostatic mechanism is also intimately correlated with the control of cardiac activity through the depressor fibers of the vagus nerve. A rise in arterial tension results in retardation of the cardiac rate and conversely a marked fall in the arterial tension causes cardiac acceleration.

The control of the arteriolar tone however does not rest entirely with the sympathetic nervous system. Hormones have some direct influence upon the medial muscle fibers. Epinephrine is markedly vasoconstrictor. Pituitrin the nitrites histamine certain bacterial toxins and many other pharmacologically active substances affect the arterial tone (and therefore the arterial tension) directly.

Hypertension then represents a disturbance or imbalance of the circulatory homeostatic apparatus. It does not involve new mechanisms and is not a new phenomenon. The state of hypertension may exist temporarily in the absence of hypertensive disease although the converse is rarely if ever true. A state of hypertension may arise from any of many sources the reactions of fear anger or excitement may result in notable but transient hypertension. With the exception of the increased tension observed in the upper extremities in contraction of the aorta however hypertension is invariably the result of increased arteriolar tonus. The primary factor irrespective of the nature of the stimulus is the arteriolar hypertonus. Hypotension conversely is usually due largely to undue arteriolar relaxation.

Results of Arteriolar Constriction It should be emphasized that hypertension due to arteriolar constriction results in reduction in the blood flow distal to the arterioles. On the other hand arteriolar relaxa-

tion increases the capillary flow to cause active hyperemia. Capillary stasis with emphatic retardation of flow creates local impairment of nutrition and the oxygen supply. For this phenomenon Riesman has coined the valuable and useful term *histoxemia* to apply to diminished oxygen supply to the cells although no true *anoxemia* need necessarily exist. It is important to remember that the greater the arteriolar constriction the poorer the capillary circulation and the higher the arterial tension. Small punctate hemorrhages into parenchymatous tissues are not unusual because of the impaired nutrition of capillary walls in severe hypertension. These physiologic phenomena are of vital importance to an understanding of both the etiology and treatment of hypertensive arterial disease.

ETIOLOGY PATHOGENESIS AND PATHOLOGY OF HYPERTENSIVE ARTERIAL DISEASE

The transition from the hypertensive state to hypertensive disease is a gradual one. At first the hypertension is variable and inconstant as time goes on it becomes more and more continuous and persistent until in the later stages of the disease the arterial hypertension is essentially irrevocable. What starts out as a purely physiologic response becomes a progressive and destructive disease. Yet we must not forget that the hypertension *per se* is but a physiologic response. Perhaps the most significant advancement in medical thought since the introduction of bacteriology has been the change in appreciation of the phenomena of disease. In the not so distant past all symptoms and signs of disease were considered to be changes requiring energetic correction. It is not long since our teachers of therapeutics devoted most of their precious lecture time to antipyretics. Now fever is induced as a therapeutic agent.

The recognition that many of the phenomena of disturbed physiology observed in disease such as fever, edema, leukocytosis and hypertension are compensatory adjustments and that they may be valuable defense reactions of the body has done more to bring logic and effectiveness into therapeutics than any other concept. The appreciation of this viewpoint is still young. There is much which must be learned as to the relative merits and demerits of various physiologic responses. To insist that all the phenomena of disease are evidences of defense reactions and therefore desirable would be just as illogical and one-sided as the older viewpoint that all such disturbances are necessarily detrimental. Each problem

must be appraised individually, both quantitatively and qualitatively. Fever may be a defense mechanism in infection, but hyperpyrexia may well be fatal. *It is characteristic of biologic reactions in general that response to stimulation is in excess of requirements.* Overcompensation is therefore the rule rather than the exception. Hypertension arises as a result of constrictor stimulation of the arterioles, the reaction of hypertonicity or spasticity of the arteriolar musculature is one of overcompensation. This particular reaction differs from most others, however, in that it does not tend to cease with the termination of stimulation. When the necessity for fever as defense mechanism against infection is over, the temperature falls to normal; when the arteriolar irritation which initiates hypertension ceases the arterioles tend to remain spastic. Apparently arteriolar hypertonia lowers the threshold of stimulation requisite to cause further contraction and thus is progressive. This progression of hypertension is usually slow, but extremely persistent.

With moderate hypertension the patient is not particularly jeopardized and active therapy would be largely unnecessary were it not for this intrinsic characteristic of constant progression with ultimate degeneration of the vessel walls. Excessive elevation of the arterial tension is frankly precarious. Thus the *duration* of the hypertension and of the factors which cause it to arise are most significant.

ETIOLOGY

The causation of anything involves three major categories of etiologic factors: (1) *Predisposing*, (2) *Provoking*, and (3) *Perpetuating influences*. These may vary greatly in relative importance in different diseases and in different instances of the same disease, but they are, nevertheless, invariably involved. For example, in acute contagious diseases the provoking causes, which include the invasion of specific pathogenic organisms and the predisposing cause of lowered resistance of the host, are more significant than any perpetuating factors. On the other hand, in the instance of cancer, the predisposing vulnerability of the individual and the powerful, though unexplained, perpetuating growth factors are more vital than the provoking or initiating irritants.

The etiology of hypertensive arterial disease is especially difficult of discovery because of the multiplicity of factors involved, because the

slow and asymptomatic early course delays discovery of the disease until after certain initiating factors have ceased to be operative and because each and every case of the disorder presents a different and individual problem. Typhoid fever is always due to the typhoid bacillus and small pox to its same specific virus. Hypertensive disease may be initiated by a great many different factors and no two cases present the same etiologic background. Those who seek *the cause* of hypertensive disease are doomed to disappointment. It is only by recognizing the fundamental principle that there are *many causes* that we can hope to progress in our knowledge. The provoking etiology of hypertension may be defined as anything which over a long period of time irritates the arterioles of a vulnerable individual. Such a definition obviously requires simplification but it reveals two essential characteristics. The importance of duration and the significant role of vulnerability. The fact that hypertension arises is in itself evidence of inherent vulnerability or susceptibility for the same sources of vascular irritation may not induce the disorder in another person. Hypertension is frequently familial and hereditary factors are being increasingly emphasized. The importance of constitutional vulnerability is recognized in many other diseases notably in hyperthyroidism, cholecystitis and cholelithiasis, migraine, mental disease, rheumatic infection and the allergic disturbances.

The clear elucidation of the etiologic factors responsible for each and every case of hypertensive disease is most important to the intelligent and effective treatment thereof for curative therapeutics depends greatly upon etiology. It is frequently impossible to do more than determine the *probable causative influences* but to say that hypertension is without cause because the causes are obscure is to beg the question. There are many known factors and probably many more which we do not as yet wholly recognize. It is not necessary that these *provoking influences* be active throughout the course of the disease for once started the processes of hypertensive disease continue under the impetus of the perpetuating factors.

Of the many sources of arterial irritation certain factors stand out conspicuously because of the frequency with which they are met with in clinical practice. These may perhaps be best presented in tabular form.

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TABLE OF ETIOLOGIC FACTORS IN ARTERIAL HYPERTENSION

I PREDISPOSING FACTORS (constitutional in origin)

A Hereditary vulnerability (often revealed in family history)

- 1 Diminished endurance of vascular structures.
- 2 Premature senescence
- 3 Hyperactivity of the sympathetic nervous system
- 4 Habitual worrier (very characteristic)
- 5 Sthenic physique

B Constitutional endocrinopathies

- 1 Thyrotoxic constitution (underweight)
- 2 Diabetic constitution (overweight)
- 3 Virilence

C Anatomic anomalies (rare)

II PROVOKING FACTORS (initiating)

A Intoxications

1 Endogenous in origin

a Metabolic

- (1) Fatigue (very significant)
- (2) Incomplete protein cleavage (allergic?)
- (3) Endocrine dysfunctions
 - (a) Hypocalcemia (parathyroids?)
 - (b) Ovarian dysfunction (climacteric)
 - (c) Hyperepinephrinemia (adrenal medullary tumors very rare)
 - (d) Pituitary basophilism
 - (e) Thyrotoxicosis (chiefly systolic)
- (4) Pregnancy ⁵
- (5) Nephritis
 - (a) Accumulation of metabolic debris.
 - (b) Reflex (?)
 - (c) Specific hormone

b Anemia

- (1) Tissue asphyxia (?)
- (2) Histanoxia nervous centers.

2 Exogenous in origin

a Metallic poisons (Hg As Pb Cu etc.)

b Alcohol and tobacco (very questionably)

c Dietary imbalance

- (1) Excesses of condiments.
- (2) Excesses of salt
- (3) Excesses of protein (rarely questionable)
- (4) Inadequate fluid intake (frequent)

B Infections

- 1 Focal infections (very frequent)
- 2 Generalized infections (especially influenza and typhoid fever)
- 3 Syphilis (very rarely)

C Neurologic factors

- 1 Increased intracranial pressure (tumors)
- 2 Worry and nervous fatigue
- 3 Psychoses

III PERPETUATING FACTORS

A Intrinsic in pathogenesis*B* Constitutional vulnerability continues Exacerbation from many sources*C* Impairment renal circulation

This table is by no means a complete list of all the possible significant etiologic factors but it serves to suggest the type of search necessary to illuminate the etiologic diagnosis of any specific instance of hypertensive disease. In individual instances of the disease several factors are usually superimposed as for example multiple vascular insults from oral sepsis, mild chronic plumbism and continued anxiety. The role of psychic disturbances in the etiology of hypertension is discussed in Chapter XLVIII.

As logical curative therapy must be based upon etiology, cognizance of the etiologic picture is essential to proper therapy. Many of these factors are amenable to therapeutic correction; others are not. Maladjustment of the diet, foci of infection, anemia, certain endocrine disturbances and exogenous intoxications are amenable. Hereditary predisposition, permanent renal impairment or past infections with permanent sequelae are irreparable and irrevocable. These aspects of the etiologic picture are significant in evaluating the prognosis.

Perhaps specific illustrative case examples may serve to further clarify the etiologic problems.

CASE EXAMPLE Mr. F. S., aged 53, battery worker and chronic alcoholic. Complained of headache, blurring of vision, loss of appetite and some unsteadiness of gait. Two acute attacks of lead colic in the past ten years. Married 20 years, wife pregnant three times but all infants stillborn. Physical findings included pallor, gross oral sepsis and gingivitis, dilation of aortic knob and loudly ringing aortic second sound. Neuritis in the upper extremities. Arterial tension 240/122. Hemoglobin

64 per cent Traces of albumin in urine and relative fixation of specific gravity with a maximum of 1.018 on the renal concentration test Family history unknown

Etiologic impression

- 1 Chronic plumbism
- 2 Anemia
- 3 Oral sepsis
- 4 Secondary chronic renal impairment

Specific etiologic therapy possible because of these data

CASE EXAMPLE Mrs E W aged 26 Four months pregnant with first pregnancy at first prenatal examination Arterial tension 170/110 pulse 76 Heart apparently normal Moderate anemia History of severe scarlet fever as a child knew of no nephritis Family history negative Clinical renal function studies revealed extensive renal functional impairment.

Etiologic impression

- 1 Chronic post scarlet fever nephritis
- 2 Preexistent hypertensive disease exacerbated by pregnancy⁵
- 3 Anemia.

Therapy suggested by these impressions

- 1 Termination of pregnancy before irrevocable damage is done by the pregnancy
- 2 Antianemic therapy

CASE EXAMPLE Mrs C C aged 60 housewife four pregnancies Overweight Complaints due to early cardiac decompensation Very low fluid intake for several years for cosmetic reasons—pedal edema from varicose veins Uneventful climacteric at 48 Family history revealed two instances of apoplexy one of congestive heart failure one of angina pectoris two diabetics and one pneumonia death in her own and previous generation Recent severe anxiety and insomnia during care of her husband following crushing injuries in automobile accident Economic strain since his death An habitual worrier as were all her family Blood normal and no appreciable impairment of renal function Amyl nitrite test revealed that hypertension was almost wholly spastic and therefore presumably rather recent

Etiologic impression

- 1 Hereditary vulnerability to vascular disease
- 2 Obesity
- 3 Anxiety
- 4 Fatigue
- 5 Inadequate fluid intake

Therapy suggested by these data

- 1 Increased fluid intake
- 2 Rest and reassurance of anxiety
- 3 Judicious application of sedatives
- 4 Weight reduction program

CASE EXAMPLE A woman aged 50 complained for several years of sour stomach and excessive belching particularly after heavy meals. Two years ago she developed some edema of the ankles and paroxysms of dyspnea unassociated with exertion. Her blood pressure then was observed at 130/90. For these last two years she complained of attacks consisting of epigastric distress, dyspnea, heart consciousness, headache and vertigo. These attacks were becoming increasingly frequent and severe. Observation of her arterial tension between attacks showed moderate elevation (neighborhood of 160/100) but *during* her episodes of weak spells readings of 250/130, 280/160 and 220/130 were obtained. Her pulse was rapid. The heart was not enlarged, urinary findings normal. Continued observation in the hospital showed further violent and excessive fluctuations in her blood pressure. Cholecystitis was the diagnosis of her long-standing indigestion and medullary tumor of the adrenal was suspected as being responsible for her typically paroxysmal hypertension. Before operation was accomplished the patient died of cerebral apoplexy. A large medullary adenoma of the left adrenal was found at autopsy as well as a purulent gallbladder.

These few cases illustrate typical problems encountered in clinical practice and serve to emphasize the importance of etiologic diagnosis to logical therapy. It is *not* the intention to imply that the therapy suggested by the etiologic impressions is the *only* treatment, but that these specific measures are significant. We must constantly keep in mind that the presence of hypertensive disease implies vulnerability to arteriolar excitation and that therefore recurrences and exacerbations may arise from a great many provocative influences. One set of provoking circumstances may be controlled when a new etiologic factor starts an acute increase in the generalized arteriolar constriction. We must therefore be constantly alert for new sources of vascular injury.

PATHOGENESIS

Hypertensive arterial disease invariably starts with a continuation of transient arterial hypertonia. As we have just seen, the increase in arteriolar tone may result from anything which stimulates or irritates the arteriolar musculature in a vulnerable individual for any length of time.

If the irritation is relatively persistent, continuous hypertonia results and hypertrophy of the medial muscle tissue follows as the first step of hypertensive disease. If the irritation be but briefly transient and the individual not constitutionally vulnerable, a temporary state of hypertension will arise, to be followed by return to more normal circulatory conditions after the subsidence of the irritation. Continuous constriction leads to the muscular hypertrophy as a result of the increased work of the muscle cells. With hypertrophy the same degree of stimulation produces an exaggerated response and the tendency to hypertonia becomes more and more a fixed habit. Prolonged continuous spasticity results in fatigue of the muscle fibers. This renders them hyperirritable. Fatigue, up to a certain though ill-defined point, reduces the threshold to stimulation and there results a vicious circle. Spasticity causes fatigue and fatigue encourages further spasticity. Fatigue must not be confused with exhaustion, where response to stimulation diminishes or ceases altogether. Changes in lactic acid content and other chemical imbalances contribute to the chronic fatigue of the muscle cells. This vicious circle is extremely significant as a perpetuating factor in hypertensive disease for it explains, in part at least, the tendency to continuous gradual progression of the disturbance even though the original provocations have ceased to exist.

With the persistence of hypertonia over a long period of time (years), certain arteriolar muscle fibers become exhausted. Exhaustion and the subsequent degeneration of these scattered cells permits of their replacement by collagenic connective tissue. This fibrosis is not an invasive or aggressive process on the part of the connective tissue, but a perfectly normal response to parenchymal degeneration anywhere in the body. The gradual replacement of the muscular tissue through fibrosis may well be considered a protective mechanism by which the weakened arteriolar walls are being strengthened by the scaffolding of collagenic fibers. Continuation of these changes insidiously leads to arteriolar sclerosis, the end point in the pathogenesis of hypertensive arterial disease. It usually requires many years before such arteriolar sclerosis becomes extensive.

The functional and anatomic changes in the arteriolar media briefly described above are perhaps better visualized by study of the diagram in Figure 1. This concept of the pathogenesis of hypertensive disease³ has proven to be a most useful working hypothesis for it offers the pragmatic advantages of unity, simplicity and practicality in explaining all the

varied and often conflicting information anent the physiologic changes of this disease

The essence of this concept of pathogenesis in nowise conflicts with the new and stimulating work of Goldblatt and his collaborators⁶ which

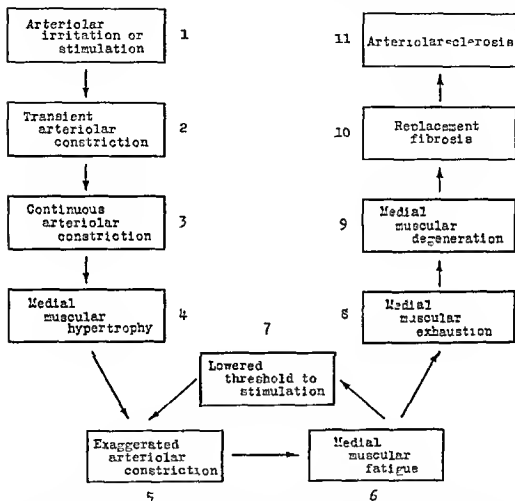


FIGURE 1 Diagram of the pathogenesis of hypertensive arterial disease. Shaded frames represent the irrevocable anatomic changes and the vicious circle which is largely responsible for the perpetuation and progression of the disorder. Steps 1 to 7 are reversible and amenable to correction; steps 8 to 11 are irreversible and permanent. (Modified from Reference 3)

has reemphasized the rôle of the kidneys in the causation of hypertension. If renal ischemia or hypoxia is an exciting cause of generalized arteriolar constriction, as the experimental data indicate, then the concept of a vicious circle which perpetuates the disorder is confirmed: for the greater the constriction of the renal arteries the poorer is the renal cir-

ulation, whereas, increase in the proximal arterial tension will tend to overcome this histanoxia. The relationship of renal disease to hypertension is two fold; renal impairment may cause hypertension, though the mechanism by which this is brought about is not clear, and also, hypertension due to arteriolar constriction adversely affects the renal functional efficiency.⁷

The pathogenesis explains many clinical phenomena. It elucidates why the provoking etiology may be *any* prolonged arteriolar irritation; the consequences will be the same. It lends weight and logically explains the clinical fact that *duration* of such irritation is of even greater significance than the intensity thereof. Acute nephritis with hypertension may result in medial thickening, but if the intoxication subsides promptly this hypertrophy recedes.⁸ It is evident from the diagram that the disease does not become self-perpetuating until arteriolar fatigue becomes involved and fatigue implies prolonged hypertonia. Prior to steps 6 and 7 in the diagram the processes are reversible; beyond that, irreversible and irreparable. Hypertensive disease is *progressive*. There is no tendency to spontaneous remission.⁹ Development is slow, but emphatically persistent. The vicious circle of the pathogenesis reveals why this is so. Recognition of this factor in therapeutic management is essential; prolonged *arteriolar rest* is the only answer to the important element of medial muscular fatigue.

The rate and distribution of arteriolar degeneration varies greatly in different individuals. The successive phases are the same, however. Extremely rapid progression is observed in so-called "malignant hypertension." This differs from the commoner hypertensive disease only quantitatively, not qualitatively, for the etiology, pathogenesis and pathology are the same. Only the rate of progression is greatly accelerated; severe arteriolar sclerosis may manifest itself in one to three years after the onset in contrast to the usual period of 10 to 20 years. The precise reasons for this variation in rate are unknown, but apparently the chief variant is that undefinable something: Susceptibility or intrinsic vulnerability. Youth is also a factor, for as a rule the greater the age at the time of onset the slower is the progression. This dictum is equally applicable to many other geriatric or degenerative diseases such as gout, diabetes and malignant neoplasms.

The explanation of why the arteriolar degeneration proceeds at different rates in various parts of the body is also obscure. Certain areas appear to be sites of predilection toward more rapid arteriosclerosis. The renal vessels are almost invariably involved. The arterioles of the spleen, pancreas and brain are involved with diminishing frequency and intensity in the order named. Thus there may arise many diverse syndromes depending upon the site of greater arteriolar impairment despite the fact that a common and basic pathogenesis occurs in all instances. The clinical symptomatology depends not upon the hypertension *per se* but upon the local histanoxia. Symptoms arise from the circulatory failure of this or that structure and the symptoms will depend upon which structure is most affected and how rapidly the ischemia is brought about. It is both illogical and unnecessary to assume that the many divergent syndromes represent separate entities. Hypertensive disease has clinical unity in its pathogenesis.

THE STAGES OF HYPERTENSIVE DISEASE

Stage	Clinical Phenomena	Steps in Pathogenesis (Figure 1)	Pathology
1 Potential stage	Undue lability of the arterial tension, excessive response to stimulation	Steps 1 & 2	None
2 Spastic stage	Continuous but variable hypertension. Lability still marked. Tension may be temporarily reduced by vasodilator drugs.	Steps 2 to 7	Hypertrophy of medial muscles of arterioles.
3 Intermediate stage	Diastolic tension more and more persistently elevated. Lability diminished. Hypertension due in part to hypertonia and in part to sclerotic narrowing.	Steps 3 to 10	Degeneration of media and replacement fibrosis in some arterioles. Changes unequally distributed: thickening and fibrosis of intima with some permanent narrowing of vessels; medial hypertrophy continued.
4 Sclerotic stage	Diastolic tension quite rigid and high. Secondary symptoms: failure of various organs due to local histanoxia. Sclerosis visible in retinal vessels; no longer amenable to therapy.	Steps 6 to 11	More generalized but still variable arteriosclerosis andendarteritic intimal fibrosis.

Stages of Hypertensive Disease Inspection of the diagram of the pathogenesis of hypertensive disease reveals how and why the disorder gradually passes through various stages to the ultimate phases of generalized arteriosclerosis. Clinically the course of the disease is clearly divisible into four stages. These correspond closely to the pathogenetic phases and like the latter tend to overlap. The continuous progression prevents sharp demarcation but they are nevertheless clinically distinguishable. They may be correlated as shown on previous page.

In the first stage the clinical and physiologic phenomena are primarily those of increased vulnerability and an unstable vasomotor equilibrium. The arterial tension is unduly variable, rising excessively upon a great variety of stimuli but promptly returning to normal levels upon cessation of the stimulation. Exaggerated emotional fluctuations are notable.¹⁰ Numerous attempts have been made to devise a test procedure with which one could compare the vasoconstrictor responses to a standardizable stimulus. It remained for Hines and Brown¹¹ to first apply cold as the stimulus. The Cold Pressor Test has proven of immense value in revealing those persons with exaggerated responses whom we may well consider as unduly vulnerable to hypertensive disease. Such forewarning is of immeasurable service in prophylaxis. It has been observed that exaggerated responses are far more frequent in children with normal blood pressures when one or both parents are hypertensive than in apparently similar children without such hereditary characteristics.^{12, 13} Similarly application of this test to pregnant women¹⁴ yields significant information forewarning of later toxemia. In order that all the data be comparable it is essential that the technic of the test be carried out in an identical manner. The technic is devised and recommended by Hines and Brown¹⁵ is therefore given in some detail.

COLD PRESSOR TEST The patient is allowed to rest in a supine position for about a half an hour. Several determinations of the arterial tension are made to obtain a basal level. With the patient still supine and with the sphygmomanometer cuff still on one arm the *opposite hand and wrist* are immersed in ice water (40°C — 39°F) for exactly one minute. The arterial tension is determined at 30 and 60 seconds after the immersion starts and every minute after the removal of the other hand from the ice water until the tension has reached its previous basal level.

In normal individuals a rise of 8 to 10 mm in both the systolic and diastolic tensions is to be expected. In those persons with potential hypertension the rise is about 30 and 20 mm respectively; a similar rise is observed in those with hypertensive disease in the spastic stage. In hypertensive patients with extensive arteriosclerosis the response is proportionately less depending upon the rigidity of the vessels.

The later stages of hypertensive disease require but little further explanation. As hypertension becomes more and more continuous the medial musculature hypertrophies. Mere eradication of the provoking etiologic factors at this stage does not suffice in arresting the progression for the perpetuating factors are now operative. Anatomic degenerative changes are insidious. The arterioles slowly become fibrotic and thus lose their power of independent contraction and relaxation. This transition is extremely slow and does not proceed uniformly throughout the body. Thus there is a long transitional or intermediate period in which both spasticity and arteriosclerosis contribute to the hypertension. In the last stage the changes are permanent, irrevocable and nonamenable to therapeutic correction.

PATHOLOGY

The anatomic pathologic changes of hypertensive arterial disease are the result rather than the cause of the hypertension. They are consequent to the wear and tear of hypertension. Arteriosclerosis follows arteriolar spasm as a degenerative lesion but is not due merely to the increased pressure of the blood for these changes do not appear in the small vessels of the arms and upper chest in cases of coarctation of the aorta despite the long continued high blood pressure. The difference lies in the fact that in coarctation there is no *arteriolar* hypertension. The fibrosis of sclerosis is not an aggressive phenomenon. There is no invasion of normal muscle tissue by collagenic connective tissue. Arteriosclerosis is best appreciated if considered as a compensatory scarring following smooth muscle exhaustion and degeneration. The medial hypertrophy of the spastic stage has been fully described ^{16, 17}

Renal injury is not invariably notable even in extreme instances of hypertensive disease. Renal disease may or may not be associated with arterial disease. When hypertension does occur with nephritis the arterial changes are of the same character as in those instances apparently free of renal disorder ¹⁸. The changes observed in parenchymatous organs

such as the brain, kidneys, pancreas, and the like, are those due to locally unimpaired circulation and nutrition

Arterial hypertension exacerbates and accelerates the degenerative changes of arteriosclerosis in the larger vessels,¹⁹ but does not initiate them. Hypertensive arterial disease is a disorder of the smaller arteries and arterioles whereas arteriosclerosis, involving the larger vessels, is an entirely different entity. Extreme arteriosclerosis can, and often does, exist with a perfectly normal level of blood pressure.

CONSEQUENCES OF HYPERTENSION

Most characteristic of the early course of hypertensive disease is the absence of subjective symptoms. The rise in arterial tension over a period of years is so gradual that compensation and readjustment keeps pace with the circulatory changes. It is remarkable that an individual may live for several years with a blood pressure of perhaps twice the normal level and yet not be aware of it. There is no sensory mechanism to inform us directly of the state of the arterial tension. This asymptomatic early course is indubitably responsible for the frequency with which early hypertensive disease is neglected. *Those disorders which "hurt" receive prompt attention*, those which do not either remain undiscovered for some time or the patient procrastinates to his own detriment.

Although subjective complaints are notably absent, objective evidence of both the hypertension and of physical depreciation is there for all those willing to take the trouble to look for it. The injury to the vital structures results from the gradually increasing histanoxia and malnutrition of the parenchymatous tissues. As previously stated, the location and intensity of localized circulatory embarrassment due to arteriolar narrowing varies greatly in different persons. Thus the symptoms and clinical phenomena will also vary widely, depending upon what tissues are suffering the most from histanoxia and how acutely this has come about.

The consequences of hypertensive disease may be broadly grouped under two major categories. (1) The sequelae of chronic and accumulative histanoxia and (2) those episodes or syndromes due to acute and abrupt interference with local circulation. Among the latter are included such dramatic consequences as apoplexy, coronary occlusion and myocardial infarction, retinal hemorrhages, angina pectoris and the acute episodes of 'cerebral vascular spasm'. Congestive heart failure is borderline

between the two categories for in hypertensive disease it is dependent upon the slow and accumulative depreciation of reserve which precedes the final acute decompensation. There is relatively little difficulty in recognizing the acute consequences but the depreciation which precedes them is occult and insidious. This depletion of reserve must be searched for.

Diagnosis to be adequate and comprehensive must include consideration of the etiology of the disorder, the nature of the pathologic lesion and the extent of functional impairment. Diagnosis therefore involves quantitative as well as qualitative evaluations. In some disorders such as diabetes mellitus and to a lesser degree hyperthyroidism precise quantitative diagnosis has proven to be of such immense practical therapeutic value that it is requisite to fully effective management. In hypertensive disease determination of the functional impairment of the two most frequently injured structures, the heart and kidneys, is not as mathematically precise. But neither is this as necessary as with diabetes.

The heart and kidneys like all other structures of the body have a large functional reserve for meeting the demands of augmented labor under stress conditions. This reserve is gradually almost imperceptibly depleted as we grow older both through the normal processes of senescence and through the innumerable insults of infections, intoxications and the like. Hypertensive disease greatly accelerates this depreciation. *Depletion of the cardiac reserve is largely asymptomatic until some undue exertion reveals the narrowing margin of safety.* Dyspnea on effort is evidence of cardiac ineffectiveness but only when the effort is unduly small. It is quite normal for dyspnea to follow excessive or violent exertion; the significant criterion of diminishing reserve is the fact that less and less effort is necessary to induce dyspnea. In frank cardiac decompensation dyspnea occurs with the exertions of mere existence even at rest. A parallel but much less conspicuously manifest situation exists in the depletion of the renal functional reserve. Depreciation of the renal reserve is asymptomatic until the excretory effectiveness falls below the requirement. Then renal decompensation or uremia occurs. The insidiousness of the renal functional reserve depletion is accentuated by the fact that the functional burdens of the kidney are much more constant than those of the heart. The cardiac burden fluctuates widely during the course of a normal day; the kidney's burden only slightly. It is only

under conditions of stress that the earlier depreciation of functional reserve are detectable This is equally applicable to the capacity of the heart, kidneys an automobile or a bank Thus stress tests which impose a greater burden upon the functioning structure, are the most sensitive in detecting early reduction of reserve In evaluating kidney injury, stress tests of renal function are often the *only* way in which early reduction of the renal reserve can be discovered

The commoner symptoms of hypertensive disease may be grouped into three divisions (1) Those referable to cardiac impairment (2) those resulting from malcirculation and histoxia of the nervous system and (3) those arising from renal failure

CARDIAC SYMPTOMS

It is justifiable to assume *a priori*, that in every instance of prolonged hypertensive disease some degree of cardiac involvement occurs The causes of this cardiac injury act synergistically The myocardium is injured by histoxia due to arteriolar narrowing as are all the tissues of the body In addition to this the heart is the *only* structure of which is demanded an *ever increasing* amount of work during the progression of this disease The higher the peripheral resistance (diastolic tension) the greater the cardiac work The magnitude of this increase in work is further enhanced by the fact that whenever the diastolic tension rises the pulse pressure increases proportionately ¹⁷

Hypertensive disease is a disease of the medial musculature of arterial structures and as the myocardium is medial musculature embryonically anatomically and functionally it is thus vulnerable to and subjected to the same sources of injury which provoke and perpetuate the arteriolar damage Furthermore hypertensive disease is ordinarily a disorder of middle or later life when recuperative and reparative potentialities are weakened and when the accumulative injuries from previous infections intoxications and the other vicissitudes of existence have left imperceptible but indelible effects on the myocardium Coincident anemia or anoxemia greatly increases the insult to the myocardium The rate of coronary circulation is in a large measure dependent upon the diastolic tension The enormously greater left ventricular hypertrophy and dilatation observed in aortic regurgitation in contrast to that found in late hypertensive heart disease may well be due to the more severe depression

of coronary blood flow in the former condition. Any impairment in the utilization of glucose creates further myocardial damage for glucose combustion is the major source of cardiac energy.²⁰ Three equally significant requisites for the proper creation of the kinetic energy of the heart muscle are Oxygen, insulin and glucose. A derith of any one of this triad disrupts the myocardial catabolism disastrously. The superimposition of all these various etiologic factors obviously accounts for the universality of the cardiac damage in hypertension.

In uncomplicated hypertensive heart disease the heart is at first *sthenic* later *asthenic* and finally *decompensated* unless some other catastrophe terminates life before the last stage is reached. The sthenic phase arises during the earlier stages of hypertensive disease when the cardiac work has been augmented by the increased peripheral resistance but before there has occurred extensive myocardial injury from *histanoxia*. The increase in vigor is purely compensatory; muscular development follows increased muscular work. The compensatory reaction is characteristically in excess of requirements. During this stage the heart is vigorous and strong; there is no consciousness of any distress and the pulse is slow and regular. There is no undue dyspnea upon exertion. There is slight left ventricular hypertrophy but no evidence of dilatation for the very gradual increase in the cardiac burden encourages compensation without overstrain. Electrocardiographic study commonly reveals only some left axis deviation and a slight prolongation of systole. The pulse pressure is increased so long as the left ventricle retains a margin of reserve. This increase in pulse pressure with a rising diastolic tension is a sound and useful physiologic criterion of myocardial reserve. A falling systolic tension in the presence of a stationary or rising diastolic tension (falling pulse pressure) is evidence of a *failing heart* particularly if the pulse rate increases. For example, an arterial tension of 170/100 pulse 80 is indicative of better cardiac reserve than a blood pressure of 150/100.

During this long sthenic phase of cardiac change we cannot consider the heart as truly diseased. More nearly do the changes imply physiologic responses to increased effort which are precursor to almost inevitable impairment later. Ultimately as the nutrition of the myocardium becomes impaired and as the burden is further increased the compensatory increased vigor is no longer able to keep pace. The cardiac reserve diminishes so slowly that the change from the sthenic to the asthenic

stage is almost imperceptible. The pulse becomes more rapid. At first this is detectable only upon effort, later even at physical rest. There appears some left ventricular dilation and frequently a soft blowing apical systolic murmur is heard. This is evidence of a relative mitral regurgitation due to stretching of the mitral ring subsequent to the dilation. Dyspnea arises upon less and less effort; the diminishing tolerance to exertion is commonly the only subjective complaint at this stage. The wishful thinking of the majority of patients causes them to attribute their short wind to extraneous factors such as tobacco, fatigue or being soft.

The intermediate asthenic stage of diminishing cardiac reserve merges by undiscernible degrees from the sthenic stage on the one hand to frank cardiac decompensation on the other. The asthenic stage may persist for many years before actual cardiac failure occurs and, of course, reappears after recovery from acute congestive decompensation. The degree of reserve depreciation is extremely variable, but the reduced functional capacity is detectable by studying the response to increased effort. The earliest evidence of diminishing reserve is always elicited under stress.

The phenomena and the treatment of cardiac decompensation are discussed elsewhere. Similarly, angina pectoris and coronary occlusion and myocardial infarction are considered in other chapters. These latter acute conditions are not infrequent in hypertensive disease, although they do occur quite independently thereof. As has been stated previously, arteriosclerosis and hypertensive arteriolar disease are distinct clinical entities, although hypertonia does accelerate the degeneration of the larger vessels in arteriosclerosis.

NEUROLOGIC CONSEQUENCES

The central nervous system is particularly vulnerable to circulatory deficiency and thus the neurologic consequences are the source of many disturbing and serious symptoms. These are extremely variable because of the high degree of functional specialization in the brain. It is sometimes extremely difficult to correlate and place in proper sequence the cause and effect relationships between certain psychic and neurologic changes and hypertension. Emotional stress, fear, anger and the like normally cause up and down fluctuations of the arterial tension of considerable

magnitude. These fluctuations are exaggerated in hypertensive individuals. Some of these relationships are discussed elsewhere but a few significant aspects warrant mention here.

There is a distinctive and characteristic hypertensive personality.¹ These people are active, aggressive and enthusiastic. They are forceful, decisive and usually intensely ambitious with a singleness of purpose which frequently leads to eminent success in their chosen careers although this may be purchased at extravagant prices in physical depreciation. These personalities resent delay and inactivity. To wait is totally foreign to their instincts. When things go wrong they are impatient to be doing something. Their relentless driving force is a potent factor inhibiting calm and analytical adaptation; they try to reconstruct their environment to their objectives rather than reconcile themselves to their environment. Restraint in physical activity is irksome and usually arouses resentment. This creates a real and often perplexing problem in therapeutic management.

Concentration and continued thought is difficult for hypertensive patients. Mental efficiency is often impaired by constant restlessness and nimble gymnastics of thought. The effort of sustained mental work thus frequently becomes increasingly fatiguing. They frequently exhibit a shortened explosive temper which with increased vigor and dynamic restlessness adds to their tendency to habitual emotional turbulence. But the most significant and constant personality traits in hypertensive persons is an exaggerated sense of responsibility and habitual worry. They appear to seek responsibilities and are constantly oppressed with anxiety concerning the wisdom of their decisions or the tragedies of others. Apprehension about their own health is exceptional for these people; with all their intensity and drive they are more of the nature of extroverts than introspective.

Perhaps it is significant that these psychic characteristics all contribute toward nervous fatigue. Such fatigue of the higher centers may possibly be a potent factor in the perpetuation of the processes of hypertensive disease. Whether the *circulatory imbalance* is responsible for these personality traits or whether the personality predisposes to hypertensive disease are open questions. It is quite logical, however, to consider that the relationship may be mutual and reciprocal, operating as a vicious circle. The typical personality pattern explains why hypertensive disease

appears to be so often selective of particularly useful valuable and energetic members of the community. This pattern is not of course an invariable concomitant of hypertensive disease but it occurs with sufficient frequency to warrant emphasis. Hypertension may appear though rarely does in phlegmatic and indolent personalities.

The chronic neurologic symptoms of hypertensive disease are so nearly identical to the phenomena observed in senility that we may consider the chronic cerebral changes as paralleling those of premature or accelerated senescence. Garrilousness insomnia impairment of memory a slow coarse tremor and dull morning headache are frequent. The impairment of memory as in the senile is most marked for recent events. Insomnia is often an annoying feature principally manifest by difficulty in getting to sleep. The morning headache accentuates the sense of fatigue on arising these patients do not feel rested. The headache is usually transient disappearing upon activity. These phenomena are often much diminished by improvement of the cerebral circulation. Histoxia of the cerebral and medullary centers will produce the same changes and symptoms whether the ischemia be due to arteriolar constriction (hypertension) arterial narrowing (arteriosclerosis) or anoxemia (anemia or relative hypotension).

Acute and/or transient symptoms arise from acute circulatory changes. Where the margin of safety is greatly narrowed relatively minor deviations may precipitate symptoms. Either acute spastic constriction of groups of arterioles or a general fall in the arterial tension to a point below that required to maintain an adequate cerebral circulation (relative hypotension) will be followed by a great variety of neurologic symptoms. In relative hypotension the pressure may still be above the usual normal levels although invariably lower than the habitual level of the individual patient.

The results of vascular spasms or of uncompensated abrupt falls in the arterial tension will depend upon the size of the area most involved the duration of the spasm or fall the efficiency of the collateral circulation and the previous state of nutrition of the tissues affected. The consequences of either cerebral spasm or relative hypotension are identical locally insufficient blood supply. Diagnostic differentiation therefore depends upon secondary observations. In cerebral vascular spasm the arterial tension is always excessively high whereas in relative hypotension

the pressure is reduced in contrast to previous levels. If the previous hypertension is of unknown degree, one must rely on other, less pathognomonic, evidences. Arterial spasms are prone to occur in the spastic stage of the disease.

Relative hypotension, on the other hand, implies some degree of permanent arteriolar sclerotic constriction of the cerebral vessels and therefore long standing hypertensive disease. The factors which induce the 'attack' aid in differential diagnosis. (1) Cerebral vascular spasm is likely to follow excitement, physical effort, digestion or fatigue, (2) relative hypotension is induced by excessive vasodilator medication, sleep narcosis, surgical shock, anesthesia (especially spinal anesthesia), coronary occlusion with myocardial infarction and the like. Symptoms from relative hypotension rarely arise unless the reduction in arterial tension is abrupt.¹⁷

The symptoms may be sensory, motor or psychic in character. Motor disturbances are the most frequent. Ataxia, motor aphasia, monoplegia, hemiplegia, impaired deglutition and choreiform jerking alarm both the patient and his family. Attacks of brief convulsions may be incorrectly ascribed to uremia. Sensory symptoms include transient and localized paresthesias, sensory aphasia, vertigo, amblyopia, anisocoria, scotomata, tinnitus, pruritus and headache. Disorientation, confusion and a simulation of parkinsonism may occur. Acute arteriosclerotic dementia may arise in hypertensive disease as well in senile cerebral arteriosclerosis. The diagnostic problems are perhaps best clarified by illustrative actual cases.

CASE EXAMPLE. Mrs. C. H., aged 70, housewife. While actively directing the activities of her maid during spring housecleaning the patient suddenly became confused and disoriented and complained of hemiparesthesia. Anxiety and tremulousness together with a sense of prostration caused her to sit down rather awkwardly so that she fell from the chair. Her family were convinced she had suffered a 'stroke'. Examination revealed a tall slender elderly woman with poor color but no cyanosis. Breathing was normal. There was no loss of consciousness but gross confusion and disorientation. Pulse was 78, regular, the second aortic sound was sharply ringing and the arterial tension 210/150. On sublingual administration of 0.65 mg. ($\frac{1}{100}$ grain) nitroglycerol her confusion vanished almost at once, though she continued to complain of the unilateral paresthesia for some hours. Her arterial tension fell with the vasodilator medication to 160/100. With bed rest, ample fluids and

sedatives her neurologic complaints completely disappeared and the arterial tension remained in the range from 160/100 to 180/110. This is a typical example of cerebral vascular spasm. The patient lived to be 74 dying of congestive heart failure.

CASE EXAMPLE. Mr. A. P., 61, professor. Hypertension first discovered ten years previously. An attack of influenza precipitated cardiac decompensation with dyspnea, cyanosis and dependent edema. He became confused and disoriented with delirium and continuous excitement. This was unimproved by sedative medication with the opiates. Dyspnea and orthopnea gradually were replaced by Cheyne-Stokes respiration. His confusion, excitement and anorexia made feeding difficult. When seen in consultation at this stage of affairs the patient was semi-comatose, wholly disoriented, cyanotic and was exhibiting Cheyne-Stokes respiration with 30-second intervals of apnea. His arterial tension was 160/110, pulse 130, cardiac findings those of acute dilatation and congestive failure. Prior to his decompensation his blood pressure had been in the neighborhood of 120/120 according to the family, who were most concerned with the mental confusion. Eye-ground inspection revealed extensive arteriolosclerosis. Oxygen inhalation, energetic digitalization and forced glucose feeding (by mouth) ultimately restored compensation. The mental confusion abruptly terminated when his blood pressure rose to 180/115—and there were no further neurologic complaints thereafter. The patient survived one year, succumbing to a repetition of the cardiac failure. This illustrates some of the neurologic manifestations from fairly prolonged relative hypotension (due to myocardial failure) in longstanding hypertensive disease with arteriosclerosis.

The dramatic catastrophe of cerebral apoplexy in a previously apparently well and vigorous person is equaled only by the similarly spectacular calamity of coronary occlusion and myocardial infarction. The immediate causes of apoplexy are cerebral hemorrhage, embolism or thrombosis. The predisposing causes are the chronic vascular diseases, arteriosclerosis and hypertensive arterial disease. Most strokes are not fatal although monoplegia or hemiplegia persists permanently. The paralysis is at first flaccid, later rigid. There may be some contracture with the development of muscular rigidity. In the upper extremities contracture is always flexor; in the lower extremities it is extensor in type. Apoplexy may recur several times, either involving different portions of the brain or by new extensions of the old lesions. The apoplectic invalid is often dreadfully helpless. He lives in constant dread of sudden recurrence of his stroke.

Circulatory injury to the visual apparatus is very common in hypertensive disease. The more frequent complaints include general blurring of vision, scintillating scotomata and transient amblyopia. Retinal hemorrhages may cause sudden and permanent unilateral blindness. The retinal vessels are directly visible by ophthalmoscopic examination. Fundus examination should be an integral part of the physical examination of all hypertensive patients. The pathogenesis of arteriolar sclerosis may be thus directly observed and invaluable prognostic and diagnostic information is thus safely and readily available. It must be recalled, however, that the rate of progression of arteriolar degeneration is not uniform throughout the body and therefore such data may mislead when the average condition of the arterioles. Generally the extent of retinal arterial change parallels the degree of cerebral arteriolar sclerosis. This is not surprising when one recalls that the retina is an integral part of the brain. Lack of space forbids any attempt to describe and/or discuss the ocular findings¹⁷ in hypertensive disease.

RENAL CONSEQUENCES

The recent and significant work of Coldblatt and his collaborators¹⁸ has stimulated a great deal of investigation. The whole problem of integrating renal disease and hypertension must be viewed from a new angle. These studies are extensively reviewed elsewhere. It appears that three types of relationships occur: (1) Renal injury may cause hypertension; (2) hypertension may cause renal injury through parenchymatous ischemia; and (3) both the renal and vascular structures may be injured simultaneously (coincidentally).¹⁹⁻²¹ The exact mechanisms by which renal anoxemia or histanoxia induce arteriolar hypertonia are not as yet understood but the most recent data²² point toward a chemical mediation in the process. Ischemic renal tissue must remain *in situ* to induce the hypertonia. The hypothetical pressor substance arising in asphyxiated renal tissue is removed by normal renal secretion. It cannot be overemphasized that if these concepts are correct (as we have many reasons to believe) a potent perpetuating influence is engendered which may well account for the persistent progression. The greater the renal ischemia, the greater the generation and/or liberation of the pressor mediator and the greater the renal arteriolar constriction with perpetuation and further aggravation of the renal histanoxia.

Though our attention is now being focused upon the kidneys as etiologic agents in hypertensive disease we must never lose sight of the fact that there are many other *active provoking etiologic factors* and that each and every case of the disease must be considered individually. Extensive impairment of the renal functional efficiency is exceptional in hypertensive disease.^{3 17 22} Renal function tests usually reveal quite normal excretory rates although specific glomerular function studies^{20 23 24} have revealed the fact that the glomerular reserve is definitely lowered. Apparently the glomeruli must work at or near the peak of their functional capacity most of the time. Injury to the glomeruli interferes with filtration and secretion more than with the free flow of blood.²⁵

Renal function tests should be utilized in the study of every case of hypertensive disease. Such tests need not involve either much equipment or expense. Although no one test procedure yields all the information desired,²³ it must be recalled that *functional impairment of the kidney always involves both the tubules and the glomeruli*. Glomerular injury inevitably impairs the tubular blood supply; tubular injury arises via the blood stream which traverses the glomerular tufts before reaching the tubules. Thus it is impossible for pure glomerular nephritis or pure tubular nephrosis to arise. The functional impairment is always mixed although frequently the injury to the one or the other structure predominates. Therefore by the application of one of the sensitive stress tests such as the urea concentration test²⁶ or the simpler and justly popular concentration test one may detect minor degrees of impairment and determine how much or little further study is desirable. Perhaps the simplest and most satisfactory routine is that of Fishberg.²⁷

RENAL CONCENTRATION TEST The patient receives no fluids or food after the usual supper until the test is completed. At 7 A. M. the patient voids and this specimen is discarded (this urine is secreted during the night). At 8 A. M., 9 A. M. and 10 A. M. respectively separate specimens of urine are collected and marked with the hour of voiding. The object of the test is to obtain specimens of urine as concentrated as possible after the body has been deprived of water for 14 to 16 hours. It is not essential that the urine be voided exactly on the hour as long as the collections fall within the period of 8 to 11 A. M.

The specific gravity of these specimens is then determined and the highest specific gravity observed taken as a measure of the concentrating capacity of the kidneys. Normally at least one specimen is concentrated

to 1.025 or more. The normal range is from 1.025 to 1.034 under these standard conditions of relative dehydration. The lower the maximum specific gravity, the poorer the renal functional reserve. Diuresis from subsiding edema, failure to have the urine at 21° C (70° F) when the specific gravity is measured and excessive amounts of albumin in the urine are all sources of error which must be guarded against. 17, 23

This is the simplest of renal function tests. It requires the minimum of laboratory equipment and skill. It is readily applied in office practice and should become a routine office test at least in cardiovascular renal problems. Obviously there is no risk to the patient.

Other desirable renal function tests include the phenosulfonephthalein test, the Mosenthal concentration dilution test, the urea clearance and inulin clearance. The techniques involved and the interpretations of the findings can not be discussed here. 23, 24, 27. The application of such tests in the clinical problems of hypertension is illustrated by the following case examples.

CASE EXAMPLE. Dr. W. J. aged 53, a practicing physician, was first seen in January, 1938. At that time he complained of undue dyspnea on minor effort and some oppressive cardiac consciousness. He was an habitual worrier. His arterial tension was 204/140. In 1932 it had been observed at 154/110. In 1928 he had passed a life insurance examination as a normal risk.

Diagnostic study (hospital) revealed

X-ray of Chest (two meter plate) Slight left ventricular enlargement and prominent aortic knob. C/T ratio 12 per cent.

Electrocardiogram Sinus mechanism. Regular rhythm. Rate 65. P-R interval 0.16 second. Q-R-S interval 0.08 second. Q-R-S slurred in all leads. T₁ small and negative. T₂ and T₃ negative. Moderate myocardial damage.

Wassermann Negative.

Blood Hb 97.4 (Newcomer)

RBC 5,150,000

WBC 9,200

Stool Negative.

Urine No albumin or sugar.

Sediment No pus, an occasional cast.

Phenosulfonephthalein

60 minutes

120 minutes

15%

5%

50%

Glomerular Function Test (Sodium Fenocyanide)

		Normal
30 minutes	98%	15%
60 minutes	11.2%	12%
120 minutes	8.4%	10%
180 minutes	12.6%	6%
Total	42.0%	13%
Maximum Renal Concentration (Fishberg)	1 014	
	1 014	
	1 020	

Urea Clearance 32.5 cc (Standard)

Inhalation of Amyl Nitrite Caused a fall of his arterial tension from 200/140 to 150/105

Diagnostic Impression

- 1 Hypertensive disease in intermediate stage (moderate sclerosis).
- 2 Progression not unusually rapid
- 3 Moderate renal impairment
Evidenced by
 - (a) Lowered maximum sp g
 - (b) Delayed fenocyanide output ²⁰
 - (c) Lowered urea clearance
 - (d) Lowered phenolsulfonephthalein excretion
 Probable nephrosclerosis
- 4 Compensated hypertensive heart disease

With increased rest reassurance absorbing investment of leisure to diminish his worrying ample fluids and some arterial sedation with his mouth subnitrate, his arterial tension gradually fell to 180/120 in March 1938, 170/110 in June, 1938, and 160/105 in August. For the last year his tension has ranged from 150/100 to 170/110 on many repeated observations.

CASE EXAMPLE. Mrs. H. P., aged 26, reported for her first prenatal examination when four months advanced in her second pregnancy. She presented no subjective complaints though her urine contained numerous pus cells and 80 mg. protein per 100 cc. urine and her arterial tension was 170/110. There was no edema. Her first pregnancy, two years previously, terminated abruptly with a violent labor of a stillborn infant at eight months after an acute two weeks illness with fever, chills, dysuria, excessive urinary frequency and pain in the right lumbar area. The acute symptoms had subsided rapidly in the puerperium. Since then she had not sought medical attention. There was no history of scarlet fever, diphtheria or rheumatic fever, but the patient stated that she had had frequent severe sore throats as a child.

The etiologic diagnosis is confused by the plethora of possible causes of this patient's hypertension and renal disease. Preexistent hypertension and nephritis exacerbated by pregnancy - with the first pregnancy terminating with abruptio placentae - could well date from the sore throats in childhood. Apparently the acute illness in the previous pregnancy had been pyelitis; the continued pyrexia suggested a chronic pyelonephritis which could cause her present hypertension and urinary abnormalities.

The Wassermann reaction was negative. The blood contained but 62 per cent of the normal content of hemoglobin; the erythroplastids numbered 3 120 000 per cmm and the white cells 10 200. The renal concentration test revealed a maximum specific gravity of 1 017. The (maximum) urea clearance was 52 cc blood cleared per minute. The phenolsulfonephthalein excretion was 40 per cent in the first hour and 30 per cent in the second hour. Intravenous pyelography showed only scant excretion on the right side with considerable distortion of the renal calyces.

These data confirmed the impression of renal functional impairment with anemia and hypertension and chronic destructive pyelonephritis exacerbated by pregnancy. Continuation of her pregnancy was considered to be extremely precarious. Therapeutic termination was advised but refused. The arterial tension rose gradually to 220/150 at seven months. At that time the renal infection became violently active; after a brief septic course the patient died. Autopsy confirmed the clinical impressions.

Most instances of hypertensive disease resemble the first of these two clinical examples. Until renal decompensation occurs renal injury may be almost wholly asymptomatic. The depletion of reserve is insidious and can usually be detected only by renal function tests early in the course of the disease. The usually accepted signs of renal disease - proteinuria, edema, casts and hematuria - are wholly inadequate criteria of the status of the renal functional capacity. Severe impairment in functional reserve may exist when the urine is apparently normal on routine examination and profuse albuminuria may occur in instances of quite adequate reserve. These phenomena are greatly influenced by extrarenal factors.^{3, 17}

Azotemic intoxication or uremia arises when the kidneys fail to eliminate the requisite amount of metabolic debris and these substances accumulate in the blood stream. Uremia is equivalent to *renal decompensation*. In hypertensive disease this may arise as a terminal event when extensive nephrosclerosis damages the kidney severely. Prior to renal decompensation the results of blood chemical analyses may be perfectly normal although the renal functional reserve is grossly depleted. There

fore reliance upon a normal blood chemistry report as an assurance of adequate reserve capacity is dangerous and illogical

PROGNOSIS

Interesting as a discussion of group prognosis might be it has little value to the practitioner of medicine confronted with the problem of evaluating the outlook for a specific case of hypertensive arterial disease. Each problem is different for the prognosis is affected by many variables. To the patient prognostication is the most important part of the diagnosis. Therapy and the severity of restrictions and limitations are often determined by prognostic impressions.

The many variable factors which must be considered include (1) The age of the patient (2) the duration of the disease (3) its rate of progression (4) the etiologic picture (5) the stage of the pathogenesis reached (degree of arteriosclerosis) (6) the status of the cardiac and (7) renal reserves (8) the possible presence of complicating disturbances such as superimposed chronic valvular disease of the heart diabetes pregnancy or secondary anemia and (9) the cooperation of the patient.

As age advances the life expectancy of course declines synchronously. But increasing age does not affect the prognosis adversely. The average therapeutic response in patients over 60 is as good or better than that of younger persons. It is a general rule that the earlier in life the degenerative diseases begin the graver is the outlook and the more rapid the deterioration. This generalization subject to the usual limitation of exceptions which try the rule is certainly applicable to hypertensive disease diabetes mellitus or gout. The onset of hypertension early in life implies marked and sometimes extreme constitutional vulnerability or active provocation as from severe nephritis. The disease progresses much more rapidly in younger persons. So called malignant hypertension usually occurs before fifty. Viewing hypertension as a compensatory phenomenon and the disease as a form of self-perpetuated overcompensation aids in the appreciation of this viewpoint.

The rate of progression of the disease is most significant in prognosis. In order to determine this even approximately it is necessary to know something of the duration of the hypertension. Because of the insidious and asymptomatic onset and early course of hypertensive disease it is usually extremely difficult to obtain accurate information. Prudent

inquiry anent previous life insurance examinations the past history and other coincidental clinical observations may reveal pertinent and suggestive data that warrant approximation of the probable duration. The rate of progression is very variable in different individuals. The appearance of evidences of arteriosclerosis within a few years of the probable onset is proof of rapid progression and justifies a much more guarded prognosis. The prognosis will depend largely upon the pace with which the pathogenic changes advance irrespective of the factors which determine this. The two major determinants of the rate of progression are the character and intensity of the provoking etiologic factors and the constitutional vulnerability of the individual.

Hypertensive disease may be provoked by a great variety of factors. Usually several causative influences are superimposed. These differ in each case. Certain etiologic factors are amenable to therapy others are not. *Local infection, fatigue, plumbism, dietary indiscretions, obesity, anemia and other similar factors are amenable to correction.* If these are considered etiologically significant in an instance of hypertensive disease the ease and safety of correction of etiology affects the prognosis favorably. If on the other hand hereditary influences, past intoxications or infections (especially past typhoid fever and/or influenza), profound personality conflicts or nephritis constitute the major etiologic background the prognosis is affected adversely. The duration of exposure to deleterious factors is also significant. Brief exposure to vasopressor influences as in eclampsia produces the *state* of hypertension. Hypertensive disease arises when such influences are prolonged. Therefore knowledge that alveolar dental infection was neglected for many years even though there is no present infection is pertinent and important. Usually the data anent etiology are but fragmentary and more presumptive than proven but it is nevertheless essential that every effort be made to gain as much information as possible.

However, the most important factor in the evaluation of the prognosis is the extent of permanent vascular injury, the determination of the stage of the disease. The detection of potential hypertension by the Cold Pressor Test has already been discussed. After the onset of hypertensive disease the pathogenic development from transient and variable arteriolar spasticity to permanent arteriosclerotic scarring is slow but persistent. The patient may be seen at any stage. The phenomena of

hypertonicity are reversible and potentially amenable to therapy. After anatomic changes have appeared (Stage 9 in the Diagram of Pathogenesis see page 1429) the processes are irreparable and irrevocable. The three stages may be distinguished even though they are not sharply separated. The variability of the diastolic tension diminishes as fibrotic scarring replaces the hypertrophied medial musculature of the arterioles. Thus persistent diastolic hypertension is more significant of arteriosclerosis than transient excessive hypertension. If the diastolic tension remains relatively fixed around 130 mm. or higher the prognosis is grave for extensive arteriosclerosis is the rule and severe nephrosclerosis is usually present. Repeated observations of the blood pressure over a period of some weeks or months are necessary to determine such variability. The patient is impatient however and demands a prompt answer to his inevitable query: What may I expect?

The relaxability of the arterioles may be determined quickly and safely by the Amyl Nitrite Test^{3 17 29 30}. The technic of this simple test is as follows:

AMYL NITRITE TEST With the patient in a comfortable position either sitting or supine several determinations of the arterial tension are made until a fairly constant basal level is reached. The patient then inhales deeply three times of a freshly broken pearl of amyl nitrite (0.3 cc. or 5 minims) while rapidly repeated observations of the blood pressure are made.

The significant observation is the *minimum diastolic* tension. This is reached approximately 20 to 40 seconds after the inhalation usually just before the intense facial blush appears. The secondary rise of tension is usually equally rapid, levels equal or higher than the preliminary readings are reached 60 to 80 seconds after the inhalation.³¹ There may occur some vertigo, sense of presyncope and palpitation. These are fleeting. If annoying to the patient the recovery period may be shortened by a whiff of aromatic ammonia.

Despite the dramatic nature of the rapid fall in blood pressure we have never observed any ill effects from the procedure. In view of the fact that amyl nitrite and related vasodilator compounds have been employed for many years by thousands of sufferers from angina pectoris without detriment untoward effects are not to be anticipated. It is notable that with extensive arteriosclerosis where such acute relative hypotension might be dangerous very little fall occurs.

As is true of any clinical test, the interpretation of the results is the most vital element. In early and therefore spastic hypertension the diastolic tension will fall to below normal levels. With gradually increasing sclerosis the approach toward normal becomes less and less. We may take 90 mm as the maximum normal diastolic tension. Thus a diastolic fall from 130 to 110 mm represents but a 50 per cent approach toward normal, a fall from 110 to 90 mm equals a 100 per cent approach toward

	Case 1	Case B	Case C	Case D
Arterial tension before test	235/140	230/130	220/130	220/120
Maximum normal diastolic tension	/90	/90	/90	/90
Diastolic abnormality	50 mm	40 mm	40 mm	30 mm
Minimum tension after amyl nitrite	185/130	160/110	160/100	130/80
Approach of diastolic tension toward normal	20%	50%	75%	100% +
Estimated degree of arteriolar sclerosis	++++	+++	+	0
Stage of disease	Arteriolar sclerosis	Late Intermediate	Early Intermediate	Spastic
Prognostic implication	Bad	Poor	Fair	Good

All four of these cases were about the same age and revealed about the same degree of cardiac enlargement. In all four instances the urine was normal. Therefore before conducting the amyl nitrite test they all appeared to have somewhat of the same outlook. But with the information gained by the test it is at once apparent that the degree of permanent irreparable damage varies greatly and that therefore the prognoses differ.

normal, although the magnitude of the drop (20 mm) is the same. In the first instance we may conclude that about half of the diastolic hypertension is spastic and the other half sclerotic in origin, whereas in the second instance the hypertension is almost wholly spastic in type.

The data of the Table will quickly illustrate the logic of interpretation. Clinical application of this test procedure has confirmed its practical usefulness. In more than 90 per cent of cases the clinical course under therapy confirms the impressions gained by this test. When the response is poor because of generalized arteriolar sclerosis no great clinical improvement

can be anticipated from any form of therapy. Failure to obtain good therapeutic results in the early purely spastic cases of hypertensive disease indicates that some active etiologic agent has been overlooked or is left inadequately corrected. The Amyl Nitrite Test does not reveal the status of any one group of arterioles such as those of the kidney or brain or heart but does yield a quick and satisfactory impression of the *average* relaxability of the vessels.

These data should be supplemented by visual examination of the retinal vessels where spastic or sclerotic changes may be observed directly. The two impressions gained may not coincide although they usually do. It should be reemphasized that as the rate of degenerative change is not uniform in all the areas of the body, localized changes such as in the retinae do not necessarily correspond exactly with the general distribution.

Since the introduction of the Amyl Nitrite Test in 1930 several other procedures have been suggested for the same objective. Beck and De Takáts³² found that the intravenous injection of 1 cc of a four per cent solution of sodium nitrite (0.4 Gm — $\frac{2}{3}$ grain) has yielded valuable and significant information. Here the response is considerably slower and thus there is more time to observe the minimum level reached by the diastolic tension. It has been suggested³³ that induction of profound anesthesia and inhibition of vascular tone by intravenous injection of pentothal sodium was a useful (?) prognostic procedure if fluctuations in skin temperature of the toes was determined by sensitive thermocouple thermometers. The risks of such profound narcosis and the unnecessary complexity of the operation involving a whole corps of assistants make its application utterly impractical.

Estimation of the cardiac reserve is of the utmost importance in proper prognostication in hypertensive disease. More than half the deaths attributable to hypertension occur as a result of cardiac defect. Though innumerable attempts have been made to devise effective tests of the cardiac reserve none of these have proven really satisfactory. The patient's story of the response to increased effort is first pointed out by MacKenzie³⁴ is probably the best criterion of the reserve myocardial vigor.³⁵ It should be recalled that though the heart may be vigorous and sthenic at the time the patient is examined, persistence of the hyper

tensive disease ultimately brings about depletion of the reserve. Both the immediate and future prognosis must be given consideration.

When extensive renal injury is found associated with hypertension the prognosis is definitely darker. The renal reserve should be determined by functional studies in every instance of hypertensive disease. Coincident or associated complicating disorders such as syphilitic aortitis, rheumatic carditis, thyrotoxicosis, diabetes mellitus, anemia and the like may influence the prognosis profoundly. Previous disease may leave a residuum of injury to this or that structure of the body so that it becomes far more vulnerable to the injury of histanoxia in hypertension. Pregnancy is a complication which alters all the problems of diagnosis, prognosis and treatment. Pregnancy invariably exacerbates preexisting hypertension and/or nephritis and these exacerbations are lasting so that progression to degenerative changes are greatly accelerated. Lack of space forbids consideration here of the problems of cardiovascular renal disease in obstetric medicine.

The emotional, intellectual and economic ability of the patient to cooperate fully may be a deciding factor in the effectiveness of therapeutic management. It is obvious that prognostication in hypertensive disease involves careful weighing and evaluation of conflicting influences. On the one hand is the knowledge of the inevitable progressiveness of the disorder and its consistent pathogenesis and on the other are the many individual variables which affect this progression either favorably or adversely.

TREATMENT OF HYPERTENSIVE DISEASE

Therapy has certain definite limitations. We can not hope to accomplish the impossible. Hypertension may be *controlled* and the progression of degenerative changes retarded but hypertensive disease is not amenable to permanent *cure*. Once the progression of events has become established in a vulnerable individual the perpetuating factors of the pathogenesis and the constitutional susceptibility of the patient preclude anticipation of cure. These factors make for progression. There is no evidence whatever that hypertensive disease is self limited or tends toward spontaneous arrest. Remissions occur but much less frequently than exacerbations. In a vulnerable patient new provoking factors may excite exacerbations long after the original set of exciting influences has abated.

The concept that hypertension is a compensatory physiologic phenomenon and thus may be desirable to the body economy or even necessary thereto modifies the objectives of therapy. If we acknowledge this concept why should we be concerned with therapeutic measures intended to reduce the arterial tension? There are several reasons. The overcompensation of physiologic responses usually ceases with the cessation of stimulation. This is not characteristic of arteriolar hypertension. The hypertonicity continues even though the provoking factors cease to be operative. Despite the fact that there is little danger for those patients with early or mild hypertension active prophylactic therapy is urgently indicated because persistence of the hypertension inevitably leads to degenerative changes in the vessels and continuously increasing jeopardy later on. Arteriosclerosis is irreparable. There is thus ample justification for treatment intended to control the arterial tension at moderate levels and retard progression. Reduction of the hypertension should be gradual so that the difficulties of relative hypotension may be avoided. In the presence of organic constriction of certain groups of arterioles the reduction of the blood pressure to theoretically normal levels may interfere still further with the blood supply to the tissues. For each individual there is some optimum range the lower limit determined by the physiologic necessity of compensatory hypertension the upper limit by the margins of safety in the circulatory apparatus. As these two limits tend gradually to draw together the situation becomes increasingly precarious.

All therapy is based upon three fundamental principles (1) *Correction of etiology* (2) *reduction of the physiologic burden of the injured structures (rest)* and (3) *aid to tissue nutrition and respiration*. This trinity of principles is universally pertinent but their clinical application does not permit of routine methods. The omission of any one of these in the planning of clinical management makes for incomplete and ineffective therapeutics.

THErapy DIRECTED AGAINST ETIOLOGY

The control of disease must be based upon the removal of the causes thereof. We may not expect to cure a sore heel due to a protuberant nail in a shoe unless the nail is removed no matter how many hot dressings or soothing ointments are applied to the heel! Obviously the first consideration is accurate etiologic diagnosis. In hypertensive disease this is never easy and often is extremely complex for every patient presents a

new and strictly individual problem. Frequently the best that can be accomplished, with present diagnostic methods, is an *approximation of some of the probable causes*. The difficulties inherent in etiologic diagnosis must never deter the clinician from making the effort to search for them. Every bit of information or hint of contributory factors may prove to be of inestimable value. In clinical practice it is the thoroughness of etiologic studies, more than anything else, that determines the effectiveness of treatment. Failure in obtaining therapeutic results, at least in early (spastic) cases of hypertensive disease, is most frequently attributable to failure in recognizing or correcting some etiologic influence. Meticulous individualization is the key to successful clinical management.

Of the three groups of etiologic factors (Predisposing, Provoking and Perpetuating influences), the predisposing causes are naturally the least amenable to therapeutic correction. By the time the patient presents the problem of hypertension it is too late to change his heredity and constitutional characteristics. Nevertheless, an evaluation of the relative rôle played by such factors is important. In the detection of potential hypertension, as by the Cold Pressor Test (See p. 1432), the discovery of such predisposing characteristics justifies the institution of certain limitations and restrictions in prophylaxis. Later, after the disorder has become more firmly fixed, an understanding of the predisposing influences will reveal valuable prognostic and therapeutic clues. For example, evidence of a strong hereditary tendency to hypertensive disease implies that hypertension may be readily provoked by relatively minor vascular irritants which might be wholly innocuous to nonvulnerable persons and that therefore special attention must be given to the search for and eradication of secondary contributing factors. On the other hand, discovering hypertension in an individual with a family history free of the disease indicates that especially active and aggressive provoking factors are operative.

The provoking etiologic factors are far more amenable to specific treatment. Removal of foci of infection, alleviation of psychotic turbulence, correction of plumbism, hematopoietic stimulation in anemia, curtailment of unwise hygienic habits, appropriate endocrine medication and insistence upon adequate time for repair and rehabilitation in the convalescence from acute infections are some of the modes of attack which may be indicated in various cases. A few case examples will serve to illustrate:

CASE EXAMPLE 1934, Mr W B, aged 43, a battery factory foreman. Arterial tension 210/130. Hemoglobin 64 per cent, moderate basophilic stippling, blood platelet count reduced to 130,000. Faint trace of albumin and 0.16 mg lead per liter of urine. Maximum specific gravity 1.018. Marked oral sepsis with many neglected dental roots. History of two attacks of lead colic. No family history of hypertension.

Diagnostic Impression Major provoking factors are chronic plumbism, oral sepsis and anemia.

Therapy

1 Hospitalization for three weeks while energetic de-leading was carried out by cautious induction of an acidosis. Followed by a high calcium diet.

2 Antianemic therapy with iron by mouth and parenteral liver extract. Continued for a year.

3 Fluid intake increased markedly and continued high.

4 Later removal of all infected dental roots.

5 High vitamin diet with concentrated vitamin B₁ added.

6 Arranged for his transfer to other employment, free of lead dust, in the same factory.

In four months the arterial tension fell to about 160/100 and has remained thereabouts since then.

CASE EXAMPLE Mrs M C, aged 43, housewife, seen in the Renal and Vascular Disease Clinic of the Central Free Dispensary, Rush Medical College. A short, obese woman complaining of marked dyspnea on exertion, some vertigo, and distress in the right upper quadrant of the abdomen. Examination revealed acute perihepatic tenderness, an enlarged heart poorly compensated and a blood pressure of 180/105. Roentgenographic studies confirmed the impression of gallbladder disease. Conservative management with sedatives, weight reduction, medical drainage of the gallbladder (magnesium sulfate orally), rest and appropriate cardiac therapy improved her condition steadily for about nine months. Weight was reduced from 180 to 160 pounds, compensation was restored and the arterial tension ranged from 170/110 to 160/90. An acute exacerbation of the cholecystitis (accompanied by a rise in blood pressure to 200/120) necessitated surgical intervention and a purulent gallbladder was removed. Thereafter improvement was more marked; a year later the arterial tension was 145/88. This case illustrates irritation from a focus of infection as a contributory cause of the hypertension.

CASE EXAMPLE Miss N M, aged 26, complained of intense restlessness, insomnia, vague apprehension, vertigo and loss of weight. Her childhood and family environment had been one of constant nervous tension and great conflict over religious views. She had been most un-

happy as a girl resorting to moderate masturbation. Since reaching maturity had been distressed by leukorrhea (later proven to be due to *Trichomonas vaginalis*) and fear of past sexual indiscretions. Recently declined to marry the man she loved for fear that marriage would be a physical failure. The basal metabolic rate was plus 9, pulse 90, blood pressure 160/102. This level of tension was observed on several occasions; it was not an isolated reading which might have been distorted by fear, embarrassment or the like. Other physical findings were normal. Reassurance, explanation, answering her unasked questions, unmasking the origins of her conflicts (religious distortion of biologic hungers), mild sedatives and persuading her to be frank with her suitor led to entire correction of her hypertension. Though she was soon happily married and her tension remained normal, she was urged to report for recheck semiannually because of the evident vulnerability of her vasomotor apparatus. Six years later there was a moderate hypertension during her second pregnancy.

These three cases may serve to clarify just what is meant by individualization in etiologic therapeutics. In many instances the provoking factors are not so readily elicited. There are certain common sources of vascular irritation which require less specific consideration. The dietary and hygienic habits of all hypertensive patients warrant patient and conscientious exploration. Unwise habits such as inadequate sleep, dietary imbalances, fatigue and excesses of one sort or another may all be contributory factors in hypertension.

Diet. Just what constitutes the proper diet for the hypertensive patient has long been the subject of much controversy. Theories and fads have come and gone. The pendulum of opinion has swung from one extreme to the other until at last it seems to have come to rest at an attitude surprisingly rational: *moderation*. The avoidance of any excess is desirable. Rigid protein restriction is no longer advocated. Liberal protein feeding does not increase the arterial tension; protein starvation may do great harm by the induction of anemia and reduction of the resistance to infection. Therefore protein sufficient for the normal metabolic requirements is necessary. The source of the protein seems to be immaterial. In obese individuals restriction of fats and carbohydrates is desirable; reduction in weight is usually accompanied by a fall in the arterial tension. Such correction of obesity thus serves two useful purposes. It reduces the load of work demanded of an already burdened heart and aids in the peripheral circulatory efficiency.

A "salt free diet" had many emphatic advocates not many years ago. Such radical restriction is no longer deemed necessary for much evidence has accumulated indicating that the salt content of the diet has a negligible effect upon vascular disease. It is true that some patients use excessive quantities of salt with their food. That is, they abuse rather than use salt. Here again, moderation is the keynote of advice. Specifically, patients are best advised not to add free salt at the table, the amount used in normal cooking should suffice. Condiments and spices are best deleted from the dietary, for the irritating volatile oils therein are direct arteriolar irritants and they add no nutritional value to the diet. Occasionally one sees cases in which an excessive abuse of "hot" spices is an active provoking factor in their hypertension.³ Meat extractives in the form of soups, gravies, broths, etc., are undesirable, they have very little food value and are prone to contain irritants.

Fluid Intake: Liberal fluid consumption is of benefit. Intake up to six liters (quarts) per day does not raise the blood pressure. Water serves both in diluting any intoxication and in decreasing the renal work. It is less work for the kidneys to secrete a large volume of dilute urine than a small volume of highly concentrated urine. Cardiac inadequacy, or a narrow margin of safety, contraindicates large quantities of fluids at any one time, but cautious administration of small amounts at frequent intervals is desirable. When the heart is sthenic or fairly well compensated, an habitual consumption of from $2\frac{1}{2}$ to 3 liters per day is suggested. Frequently hypertensive patients are encountered whose habitual consumption of fluids is far too low; intakes of $\frac{1}{2}$ to 1 liter per day are not unusual. It is immaterial how the water is camouflaged; fruit juices, weak tea, milk or Seltzer water are often more palatable than plain water until the new and better habits have become fixed.

Tobacco, Alcohol, and Coffee: The moderate use of tobacco, alcohol and coffee should not be routinely prohibited. Susceptibility to tobacco smoke is extremely variable; it is true that in some persons nicotine has a distinct vasopressor effect, but in others no such reactions are observed. It is often wise, when in doubt, to determine the blood pressure before and after smoking. In this way the patient has objective evidence which aids in convincing him of the desirability of reducing an excessive consumption of tobacco. Similar considerations apply to the temperate use of alcohol. Coffee and other caffeine stimulants are contraindicated

in the evening as they are apt to interfere with sleep, but in the morning the refreshing stimulation is desirable. It is of the greatest importance to remember that the deeply ingrained habits of elderly people are best modified but very gradually and that the abrupt interdiction of coffee, alcohol or tobacco may do more harm than good. *The psychic relaxation induced by smoking may be of considerably greater benefit than the minor detriment of some nicotine absorption.* Statistical evidence shows that the incidence of hypertension is no greater among heavy consumers of tobacco than among nonsmokers. Alcohol is likewise a sedative and is also a quickly and readily combustible fuel. It is frequently beneficial for the senile. Sudden and complete withdrawal of all caffeine from a coffee addict may have disastrous consequences. Emphasis on moderation in work and play as well as in food and drink, is all-important.

Psychogenic Factors: Habitual worry and overconscientiousness are common characteristics of the hypertensive patient. Attention to hygienic habits of sleep, exercise and relaxation and frank discussion of the advisability of lessening some burdens of responsibility frequently accomplish much in inducing highly desirable relaxation.³⁶ The wise investment of leisure³⁷ may be a potent factor in increasing longevity and in postponing disability. Exercise is beneficial, especially when it invokes fun, but the status of the cardiac reserve must be given due consideration in planning such advice.

Therapy directed against the perpetuating factors responsible for hypertensive disease has for its desideratum *rest of the arterioles*, for it is fatigue of the arteriolar musculature and the habit of continuous hypertonicity which brings about the degenerative changes. As this objective is identical with that of the second principle of therapeutics, such treatment will be considered in the next section.

THERAPY TO REDUCE THE BURDEN OF INJURED STRUCTURES: REST

Rest is the oldest of therapeutic measures. Rest has both qualitative and quantitative attributes. Rest may be localized as in the immobilization of a broken bone, or generalized, as in sleep. Psychic rest is sometimes obtained through vigorous physical activity. The effectiveness of rest depends as much upon its duration as upon its intensity. For the circulatory apparatus complete rest is impossible, (the only "vacations" the heart can get are the diastolic pauses) but reduction of the physio

logic burdens is a perfectly feasible objective. In hypertensive disease both the arteriolar musculature and the myocardium of the left ventricle are both subject to continuous and increasing fatigue. The higher the diastolic tension (arteriolar hypertonia) the greater the burden. It is these structures which require reduction of their physiologic load of work. Such rest does not necessarily involve invalidism or confinement.

The objective thus is to provide prolonged arteriolar relaxation. This can not be complete. Nor need it be. Any diminution of the hypertonia is beneficial, especially if continuous and prolonged. The primary concern is with the average arteriolar tonus rather than with transient variations. Though such arteriolar sedation is less dramatic than acute and temporary reduction of the arterial tension, it is far more valuable to the patient except in acute angiospastic emergencies such as angina pectoris. Clinical experience indicates that a gradual fall of the hypertension is more lasting; the quicker the pressure is reduced, the more likely it is to rebound in acute exacerbations.

Reduction of the diastolic tension is our guide and measure of the degree of vascular relaxation. The desideratum of arteriolar rest may be sought for by four different therapeutic approaches: (1) Psychologic measures, (2) medicinal measures, (3) physical measures and (4) surgical measures. No single remedy exists. Nor will one be found. Wise clinical management employs drugs as adjuncts, uses psychotherapy judiciously, applies physical measures when indicated and avails itself of surgical intervention when it is really called for. Frequently synergistic attack by several measures will accomplish what routinized and production-line regimes fail in doing. Less emphasis on treatments and more concern with *treatment* will improve results. The patient, not the disease or its symptoms, must be the object of our attention.

1 **Psychological Measures** The best advice is useless unless it is heeded. Mere enumeration of what the patient should and should not do is not sufficient. In chronic disorders where observation and control are matters of years, it is especially important that an intimate and whole-hearted cooperation between patient and physician be established and maintained. The potentiality of exacerbations, accelerated degenerative changes or complications is always present for the vulnerability of the vasomotor mechanisms is irrevocable. Safety depends upon vigilance and regular inventory. To gain and retain the confidence of the hyperten-

sive patient is half the battle won. This is sometimes very difficult for the majority of these people feel vigorous and well and resent the implication of disability. Unvarnished explanation of the status of their balance sheet and clear exposition of the probable outlook can do much to help the patient solve his own daily problems of conduct. The more the patient understands *why* he should do certain things and avoid others the more intelligent will be his cooperation. It is not necessary to be alarmistic indeed this may be most undesirable although these patients are rarely apprehensive about themselves. Frankly to lay the cards upon the table so far as the patient's education permits him to understand the facts always adds to therapeutic effectiveness. The viewpoint of control *vs* cure and the importance of a prophylactic attitude should be emphasized. This may involve considerable time and effort on the part of the physician but the results justify it.

The tendency to habitual worry is rarely amenable to complete correction. But with proper guidance the patient can do much to control illogical and continuous apprehension. Emotional conflicts play a most significant role in hypertensive disease³⁸ and sane and tolerant discussion of these may yield surprisingly good results. Rarely are more formal psychoanalytical procedures necessary.³⁹ The therapeutic and prophylactic values of creative hobbies,³⁷ wise investment of leisure and the psychological attributes of the hypertensive personality¹⁷ are fascinating subjects which must be regretfully omitted; the psychic factors in hypertension are fully discussed elsewhere.

2 Medicinal Measures Almost innumerable drugs have been suggested, tried, ardently advocated, found wanting and later discarded. No fully adequate medicinal agent is as yet available. Nor is it likely that *any single panacea for hypertensive disease will ever be found*. Drugs are but auxiliaries in the management to be applied individually with critical judgment of their indications and limitations.

Sedatives assist in obtaining the relaxation so necessary for rest. They should be prescribed in small doses for a long period of time; the risks of drug habituation must be kept in mind. Mild sedation to diminish the constant fretting turmoil is all that is necessary. Frequently the patients discover that their mental efficiency and their ability to maintain intellectual concentration are increased by small doses of sedatives. The bromides have proven particularly appropriate in divided doses 18 to

2.7 Gm. (30 to 45 grains) per day may be continued safely for months if the physician is aware of the possibility of bromidism. In approximately three per cent of patients, bromide intoxication required discontinuance of the medication.⁴⁰ Phenobarbital may be employed although it becomes less and less effectual with continued use.⁴¹ Intelligent administration of nembutal often breaks the habit of insomnia.

Vasodilator drugs may be divided into two major groups on the basis of their pharmacodynamics: (1) Those causing violent, immediate but very temporary vasodilation; and (2) those inducing gradual and persistent arteriolar relaxation. Of the first group, the alkyl nitrates and soluble nitrites are the most important; amyl nitrite, nitroglycerol, sodium nitrite and erythroltetranitrate. Histamine has similar effects, but is of very limited usefulness. These are all too rapid and transient in their action to be of great service in the treatment of hypertension, except in acute vasospastic emergencies. More prolonged and persistent arterial relaxation is more to be desired. For this purpose are available bismuth subnitrate, sodium or potassium sulfocyanate, acetylcholine, certain tissue extracts and several xanthine derivatives. The active principles of the several available tissue extracts are apparently closely related to adenosin or adenylic acid. These, as well as acetylcholine, must be administered parenterally, which greatly limits their application because the typical hypertensive patient feels far too well to report for injection therapy several times per week for months on end. Vascular sedation must be prolonged to be effective; rest takes time.

Of the several xanthine derivatives theophyllin-ethylenediamine (aminophylline) and the closely related glucophyllin are the most promising. Their vasodilating action, however, is largely selective and their effect is chiefly upon the coronary vessels. They do not yield the desired generalized arteriolar relaxation requisite in reduction of arterial hypertension. Their chief place is in the treatment of cardiac malnutrition and in the edema of congestive heart failure.

Thiocyanates induce prolonged vascular relaxation of the type most desired in hypertension. But therapeutically effective doses are precariously toxic. Therapy with the sulphocyanates is not safe unless the patient is under close observation. Frequent measurement of the concentration of thiocyanate in the blood, as suggested by Barker⁴² reduces the risk, but all the desirable simplicity of oral administration is lost. The

commoner manifestations of thiocyanate intoxication are muscular weakness dermatitis nausea vomiting mental confusion and disorientation. Severe cases exhibit convulsions and coma.

CASE EXAMPLE. Mrs. L. H., a housewife aged 71, was admitted for hospital study complaining chiefly of headache and vertigo. Hypertension had been known to exist for ten years. The average of many blood pressure readings was 230/130. Physical and laboratory examination showed nothing unusual—some cardiac enlargement, hemoglobin 86 per cent and a maximum urinary specific gravity of 1.023.

She was started on 0.3 Gm. (5 grains) potassium thiocyanate daily. The blood thiocyanate level rose to 4.1 mg. per 100 cc. There was no fall in the blood pressure. After two days the dosage was doubled (0.3 Gm.—5 grains—twice daily); there still was no reduction of the arterial tension although the blood cyanate content rose to 11.1 mg. per 100 cc. The dose of the drug was then again increased (0.3 Gm.—5 grains—*three* times per day) after an interval of several days. Forty-eight hours later the blood concentration was 18.2 mg. thiocyanate and the patient exhibited marked excitation with hallucinations and some nausea and vomiting. The arterial tension had fallen to 180/120, the pulse increased from about 80 to 120. The patient was seen in consultation at this time; thiocyanate therapy was promptly discontinued and a large fluid intake suggested to aid in the elimination of the drug already absorbed. Nevertheless an erythematous papular eruption appeared over the back and buttocks on the next day. The pruritus was intense. With the preexistent excitement to increase her susceptibility the patient became quite frenzied by the itching and required some restraint. On the fourth day of the eruption large urticarial wheals replaced the papular rash. Recovery from this intoxication required about ten days. During this interval the patient's blood pressure ranged from a minimum of 180/120 to 260/140 mm. Hg. After discharge from the hospital no further observations of the subsequent course were possible. The ultimate outcome is thus unknown.

This case, however, illustrates the significant fact that therapeutically effective doses of thiocyanates are dangerously close to toxic amounts. Barker⁴ states that significant toxicity begins to appear when the concentration of thiocyanate rises to 15 to 30 mg. per 100 cc. of blood. It is likewise notable that even with toxic amounts the reduction of the diastolic tension was very slight. The falling systolic pressure and rising pulse rate indicated myocardial injury.

Bismuth subnitrate offers several advantages as a mild, persistent vascular sedative. It is nontoxic, noncumulative, inexpensive and readily

0.7 Gm (30 to 40 grains) per day may be continued safely for months if the physician is aware of the possibility of bromidism. In approximately three per cent of patients bromide intoxication required discontinuance of the medication.⁴⁰ Phenobarbital may be employed although it becomes less and less effectual with continued use.⁴¹ Intelligent administration of nembutal often breaks the habit of insomnia.

Vasodilator drugs may be divided into two major groups on the basis of their pharmacodynamics: (1) Those causing violent immediate but very temporary vasodilation and (2) those inducing gradual and persistent arteriolar relaxation. Of the first group the alkyl nitrates and soluble nitrites are the most important: amyl nitrite, nitroglycerol, sodium nitrite and erythroltetranitrate. Histamine has similar effects but is of very limited usefulness. These are all too rapid and transient in their action to be of great service in the treatment of hypertension except in acute vasospastic emergencies. More prolonged and persistent arterial relaxation is more to be desired. For this purpose are available bismuth subnitrate, sodium or potassium sulfocyanate, acetylcholine, certain tissue extracts and several xanthine derivatives. The active principles of the several available tissue extracts are apparently closely related to adenosin or adenylic acid. These as well as acetylcholine must be administered parenterally, which greatly limits their application because the typical hypertensive patient feels far too well to report for injection therapy several times per week for months on end. Vascular sedation must be prolonged to be effective: rest takes time.

Of the several xanthine derivatives theophyllin, ethylenediamine (aminophylline) and the closely related glucophyllin are the most promising. Their vasodilating action, however, is largely selective and their effect is chiefly upon the coronary vessels. They do not yield the desired generalized arteriolar relaxation requisite in reduction of arterial hypertension. Their chief place is in the treatment of cardiac malnutrition and in the edema of congestive heart failure.

Thiocyanates induce prolonged vascular relaxation of the type most desired in hypertension. But therapeutically effective doses are precariously toxic. Therapy with the sulphyocyanates is not safe unless the patient is under close observation. Frequent measurement of the concentration of thiocyanate in the blood, as suggested by Barker⁴² reduces the risk, but all the desirable simplicity of oral administration is lost. The

commoner manifestations of thiocyanate intoxication are muscular weakness dermatitis nausea vomiting mental confusion and disorientation. Severe cases exhibit convulsions and coma.

CASE EXAMPLE Mrs. L. H., a housewife aged 71, was admitted for hospital study complaining chiefly of headache and vertigo. Hypertension had been known to exist for ten years. The average of many blood pressure readings was 230/130. Physical and laboratory examination showed nothing unusual—some cardiac enlargement, hemoglobin 86 per cent and a maximum urinary specific gravity of 1.023.

She was started on 0.3 Gm. (5 grains) potassium thiocyanate daily. The blood thiocyanate level rose to 4.1 mg. per 100 cc. There was no fall in the blood pressure. After two days the dosage was doubled (0.3 Gm.—5 grains—twice daily); there still was no reduction of the arterial tension although the blood cyanate content rose to 11.1 mg. per 100 cc. The dose of the drug was then again increased (0.3 Gm.—5 grains—three times per day) after an interval of several days. Forty-eight hours later the blood concentration was 18.2 mg. thiocyanate and the patient exhibited marked excitation with hallucinations and some nausea and vomiting. The arterial tension had fallen to 180/120; the pulse increased from about 80 to 120. The patient was seen in consultation at this time; thiocyanate therapy was promptly discontinued and a large fluid intake suggested to aid in the elimination of the drug already absorbed. Nevertheless an erythematous papular eruption appeared over the back and buttocks on the next day. The pruritus was intense. With the preexistent excitement to increase her susceptibility the patient became quite frenzied by the itching and required some restraint. On the fourth day of the eruption large urticarial wheals replaced the papular rash. Recovery from this intoxication required about ten days. During this interval the patient's blood pressure ranged from a minimum of 180/120 to 260/140 mm. Hg. After discharge from the hospital no further observations of the subsequent course were possible. The ultimate outcome is thus unknown.

This case however illustrates the significant fact that therapeutically effective doses of thiocyanates are dangerously close to toxic amounts. Barker⁴⁹ states that significant toxicity begins to appear when the concentration of thiocyanate rises to 15 to 30 mg. per 100 cc. of blood. It is likewise notable that even with toxic amounts the reduction of the diastolic tension was very slight. The falling systolic pressure and rising pulse rate indicated myocardial injury.

Bismuth subnitrate offers several advantages as a mild, persistent vascular sedative. It is nontoxic, noncumulative, inexpensive and readily

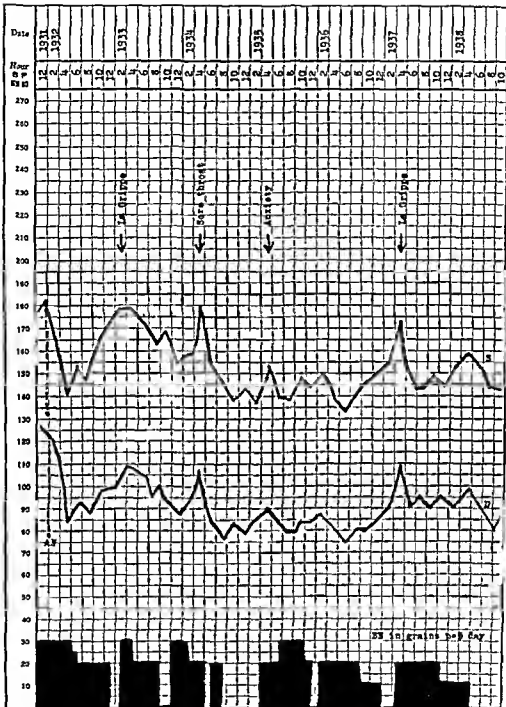


FIGURE 2 Case of Mrs. E. D. W. Course of hypertension under bismuth subnitrate therapy over a period of seven years. To conserve space on the chart the average readings of the blood pressure for each two month interval are given rather than each and every observation. Patient reported for observation about once per month over this period. Dosage of bismuth subnitrate is shown in grams per day by the shaded areas at the base of the chart. The dotted line of the abrupt fall in pressure (IV) represents the response to the Amyl Nitrite Test. The occasional total interruptions of medication were intended to prevent development of nitrite tolerance. If tolerance to the nitrite effect does develop two to three weeks' abstinence from all nitrite medication restores the responsiveness. The recurrent exacerbations due to respiratory infections reveal the vulnerability of the patient.

taken by mouth.⁴³ The low solubility of the salt permits but slow decomposition. In the bowel the nitrate ions (NO_3^-) are promptly reduced to nitrite (NO_2^-) by *B. coli*.⁴⁴ Thus minute quantities of nitrite ion are continuously absorbed. It is best administered in capsules of 0.6 Gm. (10 grains) each three times per day; tablets are too hard and insoluble. Bismuth subnitrate has proven to be a valuable adjunct in the treatment of early (spastic) hypertensive disease. The arterial sedation, however, is too mild to accomplish much in instances where active provoking factors are increasing the arterial tonus. The same limitations apply to other vascular sedatives. Such therapy can only be auxiliary to correction of active etiologic irritants.

CASE EXAMPLE. Mrs. E. D. W., aged 67, seen first in December, 1931. Hypertension had been discovered in 1928 and had been known to range between 160/110 and 210/130 since then. Strong familial tendency to cardiovascular disease. Influenzal infection in 1926, most probable active provoking factor. Renal function adequate (maximum sp. g. 1.022). Response to Amyl Nitrite Test excellent (fall from 190/125 to 130/80). Clinical course and therapy shown in accompanying chart (Fig. 2). Patient still living and as vigorous as an age of 75 years permits her to be

Many other drugs have been tried. One by one they have been or are being discarded. Some are still heralded by their manufacturers with more enthusiasm than scientific accuracy. Amorous mistletoe and repellant garlic, bitter iodides and sweet watermelon seeds! Calcium and cobalt salts have had their advocates but have been found wanting. Perenteral magnesium sulfate reduces both the intracranial and arterial pressures. It is useful as a dehydrant in some of the complications of hypertensive disease such as retinal exudates or cerebral edema. The elimination of this salt may be greatly delayed by nephritis.

3. Physical Measures. Warm baths, massage, sunshine and congenial noncompetitive sports all may prove useful adjuncts in selected cases. Vapor baths or electric cabinet sweats are precarious whenever cardiac injury exists. Sudden changes in environmental temperatures should be avoided; a cold plunge may precipitate a dangerous arterial spasm. Massage provides many of the advantages of exercise without fatigue; it is vicarious exertion. Massage is sedative and inductive of mental as well as physical relaxation. When active exertion is prohibited

by cardiac incompetence, massage is especially valuable. Sporting activities must always be graded to the cardiac reserve.

The benefits to be derived from sojourns at spas depend largely upon the economic status of the patient and the congeniality of such an environment. When the expense is a cause for worry, the net consequence is harm. One of the greatest sources of benefit in "treatment" at such watering places is the increased fluid intake, made attractive by ritualization. Water may be had far more economically at home.

Diathermy reduces the arterial tension but this reduction is but temporary. Diathermy of the renal tissues results in no appreciable improvement in renal function. Roentgen-ray therapy directed toward the pituitary and adrenal glands has been said to result in lasting reduction of increased blood pressure.⁴⁵ The recommended doses are very small; large doses are said to induce headache, vertigo and nausea and to be less effective in lowering the tension. Hinton⁴⁵ suggests 50 r units to each side of the pituitary and to each adrenal: 120 kilovolts; 2 mm aluminum filter, 50 cm. skin target distance; 3 milliamperes for five minutes. This should not be repeated more often than once per week or in courses over six consecutive weeks. In women such radiation should never be administered closer than one week prior to an expected menses. The transient nature of the clinical results of such irradiation therapy implies that the fundamental origin of the disorder has not been reached.

4. **Surgical Measures:** Surgical therapy of hypertensive arterial disease has recently been exploited with much ill advised enthusiasm. Bilateral section of the anterior and posterior nerve roots from the sixth thoracic to the second lumbar segments after laminectomy has been done in attempts to deprive large vascular areas of their vasomotor innervation and thus control hypertension.⁴⁶ Many other neurosurgical experiments (such as resection of the major and minor splanchnic nerves) have also been performed on patients. Animal experimentation has now shown the futility of such therapy.⁴⁷ The clinical results, if viewed after intervals long enough to be significant, are woefully disappointing; reduction of the mean diastolic pressures by 5 to 10 mm Hg following extensive sympathectomy. Such pathetic "accomplishments" certainly do not justify the considerable surgical risks involved.

Similarly disappointing and even more radical have been the trials with subtotal adrenalectomy and de-innervation of the adrenal glands.⁴⁸

That the therapeutic results are utterly negligible is not surprising if one recalls the invariable failures of the many attempts to show that there is more than a normal amount of epinephrin in the blood of hypertensive patients. Hypertension is not a manifestation of hyperepinephrinemia except in the few and extremely rare cases of violently fluctuating hypertension due to adrenal tumors. For such cases surgical intervention is logical and the results are dramatic. But adrenal tumors account for less than one instance of hypertension per hundred thousand cases of the disorder! Surgical adventures such as these reflect more glory upon the courage of the surgeons in rushing in than upon their sound clinical sense.

Surgery, however, has its proper place in the treatment of hypertensive disease. Certain aspects of thyroid and cardiac surgery are discussed elsewhere in this volume. The removal of foci of infection (See Case Example p. 1456) may often prove to be the turning point in a knotty therapeutic problem.

AID TO TISSUE NUTRITION AND RESPIRATION

This third and last principle of therapeutic attack is all too frequently neglected. In hypertensive arterial disease improvement of tissue respiration and/or nutrition are of particular importance. It is but necessary to recall that *all the damage done by hypertensive disease results from interference with the nutrition and respiration of the parenchymatous tissues* consequent to impairment of the circulation. The greater the arteriolar narrowing the higher the diastolic tension proximal to this constriction and the *poorer the capillary circulation peripheral to the arterioles*. The consequences of hypertensive disease are attributable to histotoxicity of important tissues. If anoxemia be superimposed upon such circulatory deficiency the injury to vital structures is tremendously enhanced. This is just what occurs when anemia or cardiac inadequacy coexists with hypertension.

Anemia and hypertension are frequently observed in the same patient. Such coincident or related anemia invariably aggravates the tissue damage. It is not logical to expect normally effective physiologic functioning of tissues whose supply of oxygen is inadequate. Therefore correction of any coexistent anemia, even if but of minor degree, is urgently desirable. It is often the greatest therapeutic aid which can be given the hyperten-

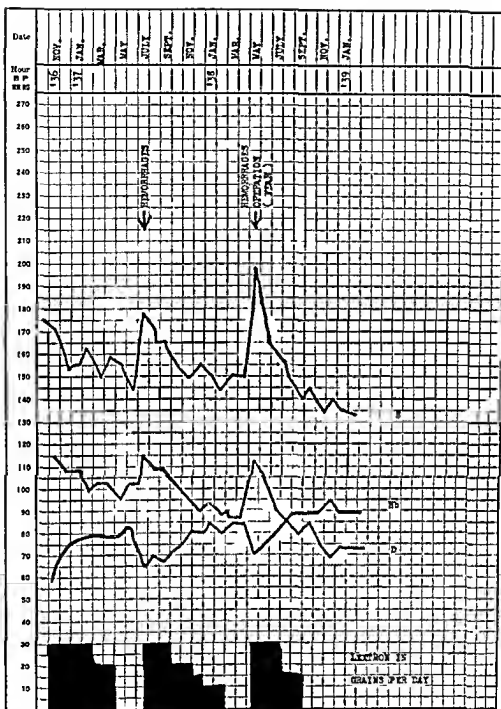


FIGURE 3 Case of Mrs. A. E. Course of hypertension and anemia over a period of two years. Anemia originally due to hemorrhages from hemorrhoids. Such hemorrhages recurred twice during the period of observation. On the second occasion hemorrhoidectomy was performed. Part of the excessive rise of the systolic pressure at the time of the operation may be attributed to fear; the patient feared surgery greatly. Medication with lextron (Lilly) indicated at base of chart by shaded areas in grains per day. It is notable that as the hemoglobin content of the blood increased the arterial tension fell. This inverse relationship is most conspicuous with the diastolic pressure.

sive patient Treatment limited to correction of anemia will frequently induce lasting reduction of the arterial tension as shown by the following illustrative case history Anemia unquestionably has some as yet improperly understood etiologic relationship to arteriolar hypertonia

CASE EXAMPLE Mrs A E housewife aged 52 complained of lassitude morning headaches apocamnosis vertigo on bending and increasing dyspnea on effort (climbing stairs) Hypertension (172/110) secondary anemia (Hb 60 per cent) and bleeding hemorrhoids were the only significant clinical findings The history revealed nothing which aroused suspicion as a probably provocative agent for the hypertension The family history was excellent Urinary findings were normal

Therapy was directed toward control of her hemorrhoidal bleeding (bland but anticonstipating diet) and correction of her anemia with Iextron (Lilly) The clinical course is revealed in the chart of Fig 3 Hemorrhoidectomy was advised when hemorrhages recurred but was at first refused Upon the second recurrence the patient consented to operative intervention Her emotional reaction to the idea of operation is well revealed by the acute rise of the systolic blood pressure With the increase in hemoglobin content of her blood and the reduction of the arterial hypertension the original subjective complaints gradually disappeared It was the reappearance of these rather than the rectal bleeding which convinced her of the desirability of surgical treatment

This case illustrates the definite but unexplained etiologic association of hypertension and anemia In view of the recent experimental work connecting hypertension with renal ischemia such observations are most suggestive

Relaxation of spastic arterioles also improves the tissue circulation Therefore reduction of the arterial tension through arteriolar dilation is doubly indicated To reduce the physiologic burden on the circulatory apparatus and to aid tissue respiration If the renal arterioles are dilated by such therapy improvement of the renal function follows Contrariwise if the arterial tension falls through diminution of cardiac force (systolic rather than diastolic reduction) and the renal arterioles remain constricted renal functional decompensation may impend Recognition of these physiological equilibria is essential to the intelligent management of hypertensive disease

Often liberal doses of reduced iron suffice in correcting moderate anemia but sometimes it is advisable to stimulate hematoipoiesis with liver extracts parenterally The hemoglobin content should be rechecked

at regular intervals because recurrence of anemia is common.⁴ We should cease considering as normal hemoglobin concentrations around 80 per cent of the theoretical normal. Though many people especially those in large cities habitually exhibit such milder deficiencies this does not warrant being satisfied with conditions so definitely below those desirable. Treatment of the severe anemia of chronic nephritis is the least satisfactory and most difficult.⁴⁹ Transfusions of blood are often life saving in renal decompensation and preuremic intoxication although the benefits are all too often temporary.

The nutritional requirements of the patient demand attention. As the course of hypertensive disease is one of years the basic diet must be adequate in water, calories, salts, proteins and vitamins. The value of weight reduction for the obese hypertensive has already been mentioned as has the importance of a generous intake of water. Glucose is important to the myocardium¹⁷—whenever myocardial failure threatens a generous carbohydrate diet is indicated. Liberal administration of glucose in cardiac failure definitely speeds recovery.⁵⁰ Prolonged and radical restriction of protein below the usual body requirements (approximately 1.0 to 1.5 Gm protein per kilogram of body weight per day) is never justified and may do much harm. Proteinuria is an indication for increasing the protein intake to replace that being lost in the urine and maintain the serum protein at normal levels. Sufficient reliable data have not yet been accumulated to indicate whether or not administration of one or more of the newer vitamin concentrates has any appreciably beneficial effect in hypertensive disease. Certainly one must be assured that at least the normal requirements are met by the diet.⁵¹

SUMMARY

A thorough understanding of the etiology, the pathogenesis and the physiologic mechanisms involved in hypertensive arterial disease are requisite to intelligent therapy. The management of the patient involves many factors. It can not be reiterated too often that each hypertensive patient presents individual problems and that routine methods of treatment will always prove ineffectual. Accurate diagnosis is essential. Diagnosis is more than giving a name to the disorder. It should include detailed consideration of the complex etiology, evaluation of the functional reserve of the heart and kidneys and determination of the stage of the

disease in its orderly pathogenesis. With these data the prognosis and the methods of therapeutic management are readily determined.

Hypertensive disease, if detected early and properly treated, is a controllable malady, although it should not be considered as curable. The hypertensive patient is in no great jeopardy until late in the course of the disease. Despite the absence of early subjective symptoms, the progression toward more and more organic damage continues. Thus the therapeutic objectives are largely prophylactic—to halt the progression and postpone as long as possible the degenerative changes. The intrinsic vulnerability of the vascular apparatus to all manner of vasomotor irritants makes for frequent exacerbations and recurrences. Constant vigilance is the price of prevention. As the state of hypertension arises primarily as an overcompensation of the arterioles to constrictor stimuli, it is not necessarily wholly undesirable. Slow but enduring reduction of the arterial tension to reasonably safe levels is more to be desired than dramatically rapid but temporary diminution of the pressure. An optimistic attitude is amply justified by the therapeutic results of conscientious clinicians.

Meticulous attention to many details of management is vitally important. The three fundamental categories of therapy must not be forgotten: (1) Correction of etiology, (2) reduction of the physiologic burden of the injured structures (rest), and (3) aid to tissue respiration and nutrition. To neglect any one of these principles is to give incomplete and inadequate advice. Evaluation of therapeutic results should be based on observations extending over at least one year, preferably longer. We can accomplish most if we consider the problem as a whole, with the patient as the unit. Psychic, economic, hereditary, and environmental influences may be equally as significant as more purely physical factors. It is the patient, not the disease, that concerns us. It is wise to acquire the habit of weighing the probable benefits against the probable detriments before dispensing any advice, no matter how trivial or how serious. If the two are about equal—do not do it.

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CHAPTER XLVIII

PSYCHIC FACTORS IN ESSENTIAL ARTERIAL HYPERTENSION

By W. R. HOUSTON, M.D.

The problem of essential hypertension centers about the attempt to understand certain continuous states of contraction in the plain muscle of the arterioles. The term "essential" may suggest that it is of the essence or nature of the arteriole to assume patterns of continuous contraction, or, what is doubtless the actual case, the term may be simply a neutral one indicating that we do not understand the pathological physiology we discuss. The addition of other words, such as hyperpiesis or entasis, to describe this behavior of plain muscle only serves further to emphasize the fact that the phenomenon under discussion has puzzled physicians and that they seek, through the use of new words, some balm for a painful state of doubt and suspended judgment. So highly problematic has become the situation as to warrant a pause before going further with inquiry into the nature and pathogenesis of essential hypertension, a pause to consider by what methods the inquiry shall be instituted.

METHODS OF APPROACH TO THE PROBLEM

The correlations and integrations of physiology and behavior in man and the higher animals take place at different levels: (1) The physical-chemical level, (2) the endocrine level, which is also chemical, but assimilable to (3) the vegetative or autonomic nervous level, a level at which the observable effects are to be found in responses of plain muscle and glandular activity, and (4) the cortico sensory-motor level—the level of skeletal muscle activity, the level where arise those problematic situations for the organism that give rise to consciousness and not only to awareness of activities within the body, but more especially awareness of interactions with the more remote environment.

Up to the present time the chief concern of modern medicine has been with integrations at the first level the physical-chemical especially with the physico chemical reactions of physiology. It somehow seems more congenial to the scientific attitude to concern ourselves with the solution of chemical problems such as those involved in the study of immunology anemia renal function circulation respiratory exchange or even allergy or endocrinology than to explore those larger and more inclusive types of integration that are affected by the nervous system. It is perhaps excusable that we should turn with satisfaction to the exploration of simple problems that we should look askance upon fields of study where vagueness and uncertainty abound and where uncontrolled speculation often riots.

Before discussing details there is reason for pausing first to consider the question—At what level shall the problem of essential hypertension be most profitably approached? There exists a wide sense of discouragement as to the results of studies that have been made up to this time. In spite of the enormous bibliography that has accumulated on the subject of hypertension the volume of publications waxing and waning through the years but always large the ultimate product as measured in terms of benefit to patients in terms of increased manipulability of this situation by the physician has been small. More than one distinguished student of vascular disease has expressed the opinion that on the whole patients are rather worse off than better off since the introduction of the sphygmomanometer. *The measurements of blood pressure often serve to focus anxiety on certain figures which the patient interprets as ominous and which the doctor can do little about, save to allay the anxiety which he has occasioned.* Such a pessimistic view of blood pressure determinations the common sense of the medical profession instantly rejects just as it would properly reject the sentiment sometimes expressed that Everything will be all right if you will just throw away your thermometer. The goal to be sought is always intelligent utilization of information not blinding oneself to the facts of a situation.

METHODS OF STUDY

To review then the method of approach made to the problem of hypertension let us first consider the history—not the history of pioneering thought but the history of mass opinion. When an instrument for

measuring blood pressure was introduced it was almost immediately put to use by the doctor in every town and hamlet who was required in the course of his insurance examinations to furnish a blood pressure reading (It may be remarked that while patients may have benefited little from blood pressure determinations insurance companies have profited to the extent of untold millions) Seldom has a new and somewhat expensive method of clinical diagnosis been so promptly put to use by the entire body of physicians

In the earlier years it was generally believed that blood pressure readings furnished information as to kidney disease and at a point in the development of kidney disease when examinations of the urine showed nothing As the years went by physicians became increasingly skeptical of this conclusion and it was at this time that the conception of essential hypertension became generally accepted Important leaders in the study of biological chemistry and connoisseurs of renal disease as well united in finding that hypertension was not always due to kidney disease and through the introduction of the term *essential hypertension* acknowledgment was made that hypertension was due to some unknown factors Most physicians were not content with so negative a hypothesis and went on to the conclusion that the causative factor was neurogenic or psychogenic So the case rested the belief was that a certain portion of hypertension could be attributed to definite renal disease say 90 per cent renal disease characterized by interference with the arterial circulation in the kidney—the cirrhotic kidney the secondary contractive kidney the arteriosclerotic kidney even diffuse forms of nephritis that lead to impediment in the renal circulation whereas forms of kidney disease that affect chiefly the parenchyma (parenchymatous nephritis amyloid disease the nephroses) were not pressure-raising

Medicine however is not easily content with hypotheses as to etiology that emphasize psychogenic factors There are many records of errors that arose out of too facile acquiescence of the psychic as a cause Between 10 and 15 years ago there began to appear an increasingly large number of articles expressing the opinion that cases termed *essential hypertension* were after all renal in origin and that a sufficiently careful study would reveal evidence of renal disease It was perhaps this trend of thought that contributed to stir up fresh interest in the laboratory approach as a means of throwing light on the problem of pathogenesis

There have been four chief lines of laboratory inquiry.

1 It was found that feeding to small laboratory animals vitamin D in excessive amounts would lead not only to atherosclerosis but to hypertension. An interesting by product of these observations was that dogs are not affected by the vitamin D feeding but that the same effects can be produced in dogs as in the small laboratory animals if the dog's thyroid is first removed. This observation is of interest in pointing to a possible endocrine factor in the development of arterial hypertension but on the whole these observations seem to find no parallel in clinical hypertension.

2 Increase in intracranial pressure, presumably lessening the blood supply to the brain and producing cerebral anoxia induces arterial hypertension. Physicians are familiar with a rise in blood pressure accompanying cerebral hemorrhage. Certain lesions of the basal ganglia have been found associated with arterial hypertension a situation that suggests an analogy with Cushing's observation that peptic ulcers may be a consequence of basal lesions. In both instances, peptic ulcer and chronic arteriolar spasm there is a spasm of plain muscle that follows a lesion in the basal portions of the brain. While here there is seen a neurogenic hypertension, it is difficult to trace a similarity between these cases of arterial hypertension and the familiar clinical hypertension. However, by laboratory methods—the introduction of kaolin into the fourth ventricle—many workers have produced states of arterial hypertension in the laboratory. Acute anemia in the cerebral circulation provokes an intense arterial hypertension, *permanent decrease of cerebral blood supply* by ligation of arteries leading to the brain may induce a condition of permanent arterial hypertension.

3 A third line of experimental approach to the problem of arterial hypertension is found in the work of Heymans on the carotid sinus and the aortic plexus. This work is at present of interest because it has recently led to the nomination of Heymans for the Nobel prize. Part of this work concerns the reaction of respiration to impulses coming from these nerve centers, that which concerns arterial hypertension is of interest here.

Heymans found that excision of the carotid sinus or the aortic plexus in dogs resulted in a prompt rise of blood pressure which persisted as a continuous state. Rises from the normal of 130 mm of mercury to 250 or 300 mm are recorded. His experiments have been repeatedly confirmed.

That a rise in arterial tension should occur not through stimulating a nervous center but through its removal seems to point to an inhibitory influence of the center that is continuously operative. The center is thought of as a kind of rheostat that interrupts and retards a continuous flow of pressor influence so that when the rheostat is excluded the full

force of the pressor effect is unimpeded. It is thought that this powerful vasopressor influence has its point of origin in the cortical psychomotor hypothalamic and bulbar centers and that it is coordinated with a series of humoral and cellular factors among which are the blood supply to the sympathetic centers and the carbon dioxide and oxygen content of the blood. Heymans notes that these reflexes of cardioaortic and carotid sinus origin regulating vascular tone and arterial pressure are absent in the totally sympathectomized dog. This observation has not been always confirmed and the problem as to the exact way in which the arterial pressure is raised still remains in doubt.

However Heymans' conclusion that the mechanism of vasoconstriction illustrated in these experiments closely resembles that found in essential hypertension is open to serious question. No experimental evidence seems to indicate that the artificial laboratory situation which he has studied in any way parallels clinical histories. The only point of parallelism seems to be the fundamental thesis that impulses coming down from the psychomotor and lower centers are powerfully vasoconstrictor.

It readily can be conceived that essential hypertension is to be explained on the basis of a heightening of this fundamental vasoconstrictor influence. In fact that is just what is meant when it is said that psychic influences produce hypertension as it is generally understood and as it is demonstrated in such experiments as the use of the lie detector. There seems no reason to suppose that a failure in the cardioaortic and carotid sinus nerve aggregations occurs in the history of essential hypertension. Consequently it is not difficult to see that these studies bring us nearer than ever before to the solution of the problem of essential hypertension.

1. A fourth experimental approach is to be found in the studies of Goldblatt on the effect upon general arterial hypertension produced by throttling the renal artery. Goldblatt produced experimentally by throttling the large renal artery the kind of effect that has been recognized in the arteriosclerotic kidney, in the granular kidney, in the secondary contracted kidney, and other conditions that impede arteriolar circulation—namely, an interference with renal blood supply. The clinical conditions that throttled the renal *arterioles* lead to a type of hypertension that has long been known as renal hypertension, and it was found that throttling the *main* renal artery would likewise lead to a renal hypertension. Goldblatt's work was antedated by that of Drury, who placed tight fitting but nonconstricting bands on the renal arteries of puppies and let them grow up into renal hypertension.

This finding, however, is not by any means all that has developed from Goldblatt's study. He was able to show that the resulting hypertension was not due, as once thought, to any accumulation of pressor

substances that should have been excreted by the kidney since a significant rise in blood pressure occurred before such pressor substances could have accumulated. He showed as had been showed long ago that a considerable rise in the level of excretory products in the blood does not entail a blood pressure rise. Goldblatt as well as Harrison and others have been able to confirm the observation made 40 years ago by Tigerstedt that the kidney contains a specific vasopressor substance which Tigerstedt called *renin*. Renin is believed to be developed in increased amounts when the renal artery or the renal arterioles are throttled and an anemia of the parenchyma produced and it is this increase in renin that explains renal hypertension. Such hypertension can be developed in dogs that have been completely sympathectomized indicating that the ultimate vasoconstriction is not produced through nervous channels but humorally by direct contact an observation that is discouraging for the therapeutic application of sympathectomy to late cases of arterial hypertension. It should be mentioned that the existence of renin in the blood stream is as yet hypothetical measurable concentrations not having been demonstrated. The pressor substance in the blood is as elusive as ever so that it is now thought that renin must react with some undetermined factor to produce hypertension.

Goldblatt's work has indeed clarified our understanding of the physiological mechanisms involved in renal hypertension. But the immediate question is how do they concern the problem of essential hypertension which has long been supposed to present a new problem not included in the problem of renal hypertension. It may be surprising to some to learn that the acute interest evoked by Goldblatt's studies has led some students of hypertension to the conclusion that all hypertension is mediated by throttling of the renal arteries. This would mean to say that the other three types of experimental hypertension referred to above converge in that each of them produced a functional throttling of the renal arteries. Even if this were true—and I know of no experiments that verify such a hypothesis—the problem of essential hypertension would still remain a problem of how psychomotor and cerebral impulses were able to lead to a functional arterial throttling specifically of the kidney vessels.

In any interpretation of hypertension there are involved a number of intermediate mechanisms. For example at the sympathetic terminal on the arteriole it has been shown that a chemical sympathin (probably the same as adrenin) is formed or released by the stimulated sym-

pathetic fiber and forms an intermediate step in transmission of nervous impulse to the blood vessel. Similarly, it is conceivable that the entire renal mechanism may be an intermediate step in the production of the phenomenon of essential hypertension, but even were this admitted, there still would remain a marked difference between renal hypertension in which inflammatory or degenerative changes in the arterial supply of the kidney are the causative factor, and, on the other hand, the case where renal throttling occurs in an otherwise healthy kidney, and is merely the means of effecting changes that take origin in the central nervous system.

Looking back over these experiments, it may be seen that while they have thrown light on the physiological mechanisms by which arterial hypertension is effected, they fail to indicate the beginnings of the chain of events that terminate in what we have learned to call essential hypertension. It is evident that arterial hypertension is a mechanism which, like respiration and pulse rate, is responsive to many situations: (1) To chemical situations, (2) to different degrees of activity in the entire organism, (3) to changes in the endocrine balance, (4) to the removal of parts of the autonomic nervous system on one hand, or to stimulation of the autonomic nervous system on the other, and finally (5) to cerebral influences that are by turn predominantly motor, sensory, or emotional.

THE TIME ELEMENT

In the mass of observations made in the course of clinical and experimental inquiry on the nature of hypertension, a factor that seems quite generally to have received insufficient emphasis is the *time* factor. If attention is given to the mass of literature quantitatively rather than in detail, it will be seen that the bulk of observations concern late effects of arterial hypertension, observations made at a period in the development of hypertension when macroscopic pathological changes already have developed. The focus of interest has been those changes that are obvious heralds of dissolution. When changes become manifest in the retinal arteries when cardiac hypertrophy is evident when the picture of the arteriosclerotic kidney begins to emerge the long history of hypertension is approaching its terminus, and not only the structural changes but the course of hypertension is all but irreversible. Many palliative measures have been proposed some of almost frantic desperation to

stay the progress of hypertensive disease in its later course but in general it may be said that the nearer we get to the post mortem table the less is the prospect of doing something worth while about our problems. Inquiries tend to take on a mortuary rather than a hopeful flavor. A certain justification seems to be found for the impatience felt by many patients and some students of vascular disease with the emphasis placed on blood pressure readings.

Suppose now that it were possible to shift the focus of attention to the beginnings of arterial hypertension that our studies were more linear less cross sectional. It may be recalled that Sir James Mackenzie felt so strongly the need for the study of vascular disease as a life history rather than during a brief observation period that he abandoned his London consultation practice and took as a proper point to make his studies a small community in which it was feasible to observe the entire life history of a group of people. Sir James Mackenzie died no great while after making this move but the lesson his acute common sense sought to illustrate should not be lost.

To wait 50 or 60 years for the data of an experimental observation to be gathered is a slow business. Yet however we may bang and rattle at the door it may still be necessary to wait so long or longer before we can accumulate facts that will establish soundly any hypothesis about the pathogenesis of essential hypertension. There remains at all events the resource of attempting to analyze the record of human histories that we have already accumulated in order to observe in how far they support the following hypothesis.

Essential hypertension is a learned reaction. It is a set or action pattern, acquired by the plain muscle of the arterioles. This tendency of arterioles to become fixed in a state of contraction is developed through impulses coming over nervous paths. The chief stimulus to arteriolar contraction comes through the sympathetics but takes origin in human relationships, in a general attitude of mood and emotional tone that prevails in the human environment. That some persons inherit a greater aptitude for acquiring the attitude that leads to hypertension, that hypertension partakes of the nature of other muscular habits in that it contains a propulsive element that tends to perpetuate the habit. That to interfere for the correction of such a habit we must begin at an age when habits are reversible, when new habits can be learned. That intelligence may

hope to improve the situation (1) through instruction and persuasion inducing a conscious attempt to correct a faulty attitude (2) through plans that change the human environment That means may be found through statistical studies and through better understanding of emotional attitudes to establish the above conclusions

Attempting to select among the facts available those most relevant to this hypothesis the suggestion at once occurs Why doesn't everyone develop hypertension? What about persons who go through life with well modulated blood pressure? When one begins to turn this question over a second question suggests itself Was hypertension in the past as large a factor in medical consideration as it is today? Was arterial hypertension which now is said to carry off a fourth of the population so important a cause of sickness and death in the presphygmomanometer era? Have our measurements disclosed a condition that was always there or do they reveal an increasing menace?

In the terms of the above hypothesis the blood pressure readings point to a change in the social climate a change in the disposition of human relationships One bit of evidence that points to the existence of a change in the prevalence of arterial hypertension is to be found in the fact that Austin Flint a cardiologist of wide experience and repute spoke of angina pectoris as a very rare condition met with once or twice in several years of practice Since angina a long recognized syndrome is an index of arterial disease the inference seems justified that essential hypertension the chief factor leading to arterial disease was also rare Several years ago the late William Mayo addressing the medical section of the American Medical Association spoke of the alarming increase in fatal vascular accidents among surgeons Mayo quite definitely indicated that there was something in the surgeon's work an environmental factor which predisposed to vascular disorder but the relief that he was asking medical men to seek lay in the direction of establishing a sounder attitude of the surgeon toward his work

Social Climate and Attitude A survey of such literature as reflects the emotional attitude of people by decades and centuries strongly suggests that there has come about a change in social climate and attitude—an abandonment of the conception of the good life as being a balanced life a life in which anything too much anything in excess was to be shunned a life in which order measure proportion were emphasized

It would be idle to try to put one's finger on the spot where a change in the notion of what constitutes a good life took place but we can point to Theodore Roosevelt as the spokesman of our present conception of good life as embodied in his phrase the strenuous life. If such a change in attitude really occurred it doubtless occurred gradually and T. R.'s acclaim of the strenuous life only gave voice to an attitude already widely esteemed as praiseworthy.

(In passing a brief pause is permissible to comment on a thought that must arise in connection with the historical incident that Theodore Roosevelt succumbed to hypertensive disease at an age perhaps 10 or 12 years short of his expectancy and so illustrated pungently the merit and defects of the strenuous life if such life naturally predisposes to arterial hypertension. A case can well be made out for the idea that a life full and brief is to be desired rather than one tranquil and prolonged that the gains to our pattern of civilization would be greater if we all accepted and practiced the doctrine of the strenuous life than a less mettlesome less dangerous way of living would entail a loss. To assess the values involved in the question is scarcely within the doctor's province. The medical profession is committed to the notion that it is the doctor's province to prolong life not to inquire whether life should be prolonged. The physician can only point in the relation of cause and effect involved in a course of action.)

The suggestion has been made that a certain social climate or attitude may be responsible for a rising curve of arterial hypertension in the population of some countries and that this attitude is acquired through average social intercourse more than through any propaganda. Is such a suggestion warranted? How well warranted the suggestion is could be estimated if it were known what incidence of arterial hypertension is found in regions where a different social attitude prevails. The facts that have been gathered concerning the distribution of arterial hypertension through the world are not as well documented as could be wished. Much has been written but statements of the writers give impressions rather than massive statistics. Considerable samplings of blood pressure readings in large population groups have been recorded however and enough to support strongly the belief that great differences in the incidence of essential arterial hypertension exist.

It is said that among Negro tribes of Africa living there all their lives out of contact with the whites essential hypertension is not found

It is rarely observed in the population of India. When I went on a visit to China in 1922 I was told by the medical chief of the Peking Union Medical School that I would not find cases of essential hypertension among the Chinese. Happening to remain in China for over four years with the opportunity to observe quite a large clinical material at the Hunan Yale Hospital in Changsha, the hospital operated by the Medical School of the Yale in China enterprise, practically no cases of essential hypertension were found. I recall a single exception in the case of a young Chinese woman who had recently come to China from Boston where she had worked as a trained nurse and who had learned to use the expression "these Chinese" as designating a different sort of people, she herself being an up and coming go-getter. Arterial hypertension was found among the Chinese to be so regularly associated with renal disease that a blood pressure reading all but sufficed for a diagnosis.

Two studies that appeared in the *Archives of Internal Medicine* note the interesting observation that white men living in the interior of China gradually came to have blood pressure readings which are normal for the Chinese and which show an average systolic pressure 15 to 20 mm lower than the normal observed in America. Readings made in the course of periodic annual examinations showed a steady decline in blood pressure extending over several years after a man came to China and the old China residents generally had a systolic pressure of 100. The observation has been made that Chinese living in America have by and large the same kind of blood pressure readings as Americans. American Negroes are probably more subject to essential arterial hypertension than are the whites. It is said that observations made in Shanghai show a certain incidence of essential hypertension but Shanghai is a westernized city; anyone who has been there can tell the striking difference between the social atmosphere of Shanghai and that of an interior city like Peking or Changsha.

Several explanations have been offered for the blood pressure observations made in China. A writer interested in climatic influences tries to show that temperature changes in China are less abrupt than in western countries. This climatic difference explains the situation. This writer cannot help knowing that blood pressure among the Chinese is the same in subtropical South China as it is in Mukden where winter temperatures go to minus 40° C (minus 40° F). A Chinese peasant in

Manchuria who sleeps on a warm oven all night must experience as abrupt a climatic change when he ventures out of doors as a man meeting a norther on the western plains

It has never been shown that persons living in the equable climate of the Pacific Coast are less subject to essential hypertension than those who live in the Middle West

Diet A second line of explanation is sought in diet. People living on a diet of rice and herbs must have lower blood pressure than those eating a generous high protein diet. This explanation doesn't meet the facts for the reason that the well-to-do classes in China who are greatly given to the pleasures of the table and eat a very high protein diet have the same range of blood pressure as the half starved peasant. The westerners living in China who gradually develop the Chinese blood pressure levels had a diet scarcely distinguishable from that taken at home in the West.

Internists in America have for some time pretty well ceased attempts at dealing with essential hypertension by dietary restriction. While it is admitted that prolonged infection, tuberculosis or typhoid will lower blood pressure and that in the same way insufficient diet by depleting energy will have a similar effect, it is generally regarded as an advantage in dealing with the problem of hypertension that the therapeutic burden of selective dietetic restriction has been put aside.

One must be blind to deny that climate and diet play their part in making the individual or the group what they are. It has been repeatedly shown both experimentally and clinically that a vitamin deficiency predisposes animals and men to neuroses, but a survey of the population even if limited to America does not indicate that incidence of arterial hypertension follows isotherminal lines or abruptness of weather change nor has it shown that the needy are less subject to essential hypertension than the well fed.

Perhaps climate and diet do after all play a part in the causation of essential hypertension. Biological questions are not to be answered in terms of an absolute yes or no. It is not known just where botany ends and zoology begins. It is not even known whether viruses are living or not. We get no further in considering questions of life and man than a statement of more or less. The statement made is that it is a

good deal more true than less true that climate and diet are not important and decisive factors in the production of essential arterial hypertension

Habit and Emotional Attitude Since these simpler explanations of the distribution of hypertension in the world population have failed it remains to consider the more complex explanation involved in the conception of habit and emotional attitude. Just what do these terms mean from the standpoint of the abnormal situation characterized by pathological physiology?

WHAT DOES PSYCHOGENIC MEAN?

Before discussing this question time out must be taken to speak briefly of some unspoken presuppositions that underlie most medical thinking

Most doctors do not regard man as an animal inhabited by a ghost. In the past true enough *psychic* has been taken to mean *ghostly*, with results for medical practice that have been ghostly as Adolf Meyer pointed out years ago in his notable paper. The practical result of making *psychic* mean *ghostly* is to destroy the doctor's interest in psychic problems and corrode his sense of responsibility for the outcome of psychic situations.

When the modern physician uses the word *soul* he is not thinking in terms of simple supernaturalism of a ghostly inhabitant of the body but of something much more abstract—namely of interactions of relationships. These interactions within the body are chiefly carried out through the mediation of the nervous system. The interactions which are designated as *psychic* and which form the theme of psychology are chiefly relations with distant things for the most part with other human beings. Even thinking which might seem to be a private affair involves the use of words and words arose through communication with other men. Thinking is a kind of discourse in which the words which came into existence for the purposes of communicating with others are employed in soliloquy. We employ words as symbols and by means of them we can rehearse action.

John Dewey pointed out in his address to the internists of America assembled in St. Louis in 1937 that man does not end with his skin since those factors that constitute man as a person consist largely of interactions with what is outside his skin. Essential hypertension for instance from

the psychologic standpoint is to be regarded not as an isolated phenomenon but as the terminal manifestation of interaction with a huge social background. Taken in isolation it is bound to be misinterpreted. Taken as a physiological reaction occurring wholly within the human skin it will not be understood. No more than respiration can be understood without considering the air respired, no more than walking can be understood without reference to the sustaining earth, no more than swimming can be discussed without regard to water, can an emotional attitude be understood without considering the human beings that are involved in it.

The doctor, in so far as he becomes a scientist, naturally gets to regard relationships, interactions as something to be dealt with, just as the grammar school child gets to think of multiplication and division as something to be dealt with. What is peculiar about such things as multiplication and division is that they represent operations to be performed, the operation consisting of the development of relations between numbers. The kind of things that a student of physiology is chiefly concerned with is relationships. The doctor is likely to think of essential hypertension as a thing. In fact it is a fairly complex series of relations involving fluid in containing tubes, varying pressures of waves and current relation of vis a tergo to peripheral resistance, a relation between intraarterial pressure, air pressure in a rubber tubing, pressure in a column of mercury as seen against a calibrated scale, pressure on skin, tension in the spring as recorded by a moving needle as observed on a dial, a relation between observations made on one individual with observations made on groups of individuals. In a word, the whole affair is a question of intricate relationships, the details of which might be far more widely gone into. All this insistence on the obvious, this long-winded explanation of what everybody knows, namely, that the final figure arrived at in taking blood pressure is just a shorthand for recording relations that are developed in the course of a number of operations, is gone into for the purpose of making explicit the fundamental importance of relationship.

When we discuss psychology, we are also talking about relations. When a relation is represented by a symbol, such as the symbol for multiplication or division or the figures expressing blood pressure, we tend toward regarding a relationship as a thing. As physiologists we know that breathing means the operation of establishing relationship.

between environing oxygen and body cells. But we should remember that breathing was in Greek *psyche*, from which we have *psychology*, in Latin *spiritus* from which we have *spiritual* which represented in early ages the immaterial. Breath was that immaterial something that made the difference between the living and the inanimate. Here again *anima* means *breath* and animal is what breathes. The ancients made a physiological relationship into what we now regard as a psychological relationship. They considered air spiritual, psychic though we know air to be material for physical and chemical study.

It would be better for our thinking about psychogenic problems if we discarded the use of nouns which make things out of relationships and were to employ only adjectives since the adjective points to relationship and in fact in the usage of doctors it is words like psychic, emotional, active which are given preference over such terms as soul, emotion, movement.

It is of course natural for doctors to want to put their finger on the place where relationships are established. And so we are apt to think of the cortex with its sensory and motor branches in connection with intelligence of the thalamus and the autonomic system in connection with feeling of muscles and glands in connection with activity. But common sense tells us that walking is not understood by the dissecting muscles of the legs but only by considering an interactive relationship going on between legs and ground and that in the same way thinking does not reside in the cortex but consists in the interaction between a person and other persons and things.

The fact that the phenomenon of consciousness arises in the course of these interactions doesn't bother the doctor much because of his strong bias toward looking outward. If however the doctor thinks of consciousness he may think of it as a property of cortical activity just as contractility is a property of muscular activity. The doctor deals constantly with this property of consciousness altering the threshold of consciousness by the use of narcotics abolishing consciousness by the use of anesthetics regarding the degree of consciousness as a symptom of the ability of the organism to maintain favorable relations with environment. The whole matter is an affair of relationships and can be thought of not in the simple relationships of pushing and pulling, knocking into and throwing back, leaning toward and away as we have psychological rela-

tionships enshrined for us in the etymology of our ordinary speech but as existing more on the physiological models of the magnetic field and the wave transmission of sound and light by means of which relations with distant objects come about

EMOTIONAL RELATIONS

Thus digression was undertaken to make more explicit the doctor's position in regard to what is meant by psychic relations as being more complex but not more mysterious than other groups of relations with which we constantly deal. What is meant then by saying that blood pressure is influenced by emotional attitude?

Certain emotional reactions can be studied in the laboratory as Cannon has studied the emotional reactions of cats and dogs. These brief violent emotional reactions measurably affect blood pressures. They are not the kind of emotional reactions that lead to chronic arterial hypertension; they are the kind measured by the lie detector.

All students of hypertensive disorder have recognized cases of emotional hypertension cases in which as a result of long emotional excitement or conflict the patient shows over days, weeks or months an arterial hypertension which disappears when the emotional excitement has abated or the conflict is resolved. These instances of emotional hypertension while they throw light on the subject of essential arterial hypertension are plainly not the situation existing in the majority of cases of essential hypertension. In fact the existence of this pretty well defined group tends rather to obscure than to illuminate in the conception of emotional attitude as productive of essential hypertension.

What is meant by emotional attitude as a continuous state is an habitual disposition of the thalamic autonomic component in human activity, a certain *set* given to activity, a set or reaction pattern that is produced by the environing social habits. Doctors because of their preoccupation with physiological reactions going on within the skin seldom take enough account of how much personality is a matter of social contact of human relationships. We doctors belong to what William James called the tough minded interested in crude facts in all their varieties insufficiently aware that the facts they deal with are largely relationships and especially unaware of the enormous influence on themselves and on their patients of social relationships.

Since arterial hypertension has been spoken of as a habit that is *learned* let us direct attention to the role of the social environment in the formation of habit. The habit most characteristic of man is his use of words. Without words thoughts would be few and vague if any, and words are a social heritage. Like every other activity, the use of words involves intelligence, feeling, and action, all three working together. But on the muscular side we see that when we have learned to speak one language the muscles involved in speech acquire such a set that it is difficult when the muscular set employed in speaking one language has been thoroughly learned ever to acquire a new muscular set that will enable one to articulate correctly a new language. The persistence of a muscular set is seen not only as between different languages but between those speaking the same language in different places; the difference in the speech habit of a New Englander, a Southerner, and a Midwesterner. An American going to England often acquires British speech habits to the dismay of his friends when he comes back home. His muscular behavior patterns have been changed, not purposely, by social contagion.

Not only our habits of speech but our patterns of thinking and feeling are for the most part learned from our associations with men. It is hardly necessary to say that if the Hitler youth or Bolshevik youth had been reared in an American home his emotional attitude toward world affairs would be very different from what it is. Only a little reflection is needed to convince anyone that the role of intelligence in forming emotional attitudes is small as compared with the contagion of attitude that comes through close human relationships. Since character is built up of the interaction of habits that have been learned, since activity falls into patterns made up of habits, since personality is largely constructed out of habitual ways of acting, it becomes inherently plausible and probable that a muscular set, a pattern of muscular reaction, such as is seen in essential hypertension, should be acquired through social relationships.

Physiology and psychology consider a living creature in action. It isn't necessary to ask the question, *Why is there action?* Merely to say that the creature is living implies action, interaction with his environment. In man, while never forgetting that we are talking about an organic unity, we are accustomed to emphasize, as the occasion arises in discussion, one of three phases of his nature—intelligence, feeling, and

action. When he is awake all these three are unitedly and cooperatively at work.

How these three phases cooperate is a problem of psychology and John Dewey was not merely flattering the medical profession when he said that as doctors we occupy a very favorable strategic position for considering this problem. It is not an accident that the leading contributions to the problems of psychology in the past generation have been made by physicians. By Pavlov, who calls his work on conditioned reflexes

A Study of the Physiology of the Cerebral Cortex, though this emphasis on the cortex may easily lead one to forget that he is also studying a feeling, the feeling of hunger in his dogs and in action, the action of a gland in secreting saliva, in other words he was studying the interaction of the whole dog with his environment and disclosing many interesting and significant analogies between these simple and more analyzable situations in the dog and the vastly more complex interactions of man with his environment. Another physician, Freud, has enriched our understanding and deepened our insight into the problem of the interaction of conflicting emotional habits. It would be noted that both of these great students of behavior were dealing with habit situations that are learned. Both were interested in showing the details of how habits are learned. In the studies of both it seems clear that first comes a feeling, second cortical operation and last some form of activity. Pavlov's work is analytic of a simpler situation. Freud begins with a situation already extremely involved. Both are concerned with habits—Pavlov with habits in formation, Freud with habits long formed.

Given a living creature in action, his activity, if it is not to be chaotic and ineffectual, must be directed along certain channels, must be effectively canalized. Activity for the most part follows patterns determined in the process of evolution. Physiological reactions are not generally learned, though unfortunate variants in physiological reaction are sometimes learned. One of the most important questions that a doctor has to decide clinically is the question: How much of certain reactions is learned and how much is inborn?

He notes that in the lower animals complex patterns of behavior develop without what we call learning—running, flying, swimming, building of nests by birds, dams by beavers, honeycombs by bees. When we think of the bee and the ant it looks as though the perfect organism

might be one without feeling or intelligence one possessed only of patterns of activity perfect reaction patterns to every stimulus it looks as though feeling represents a hindrance or impediment in the smooth continuous flow of well instituted habits a disorderly clash in habit as though feeling were a kind of malaise and in the same way it looks as though conscious intelligence were a malaise and arose through a threat to the adjustment of activity It is a common saying that we do best what we do unconsciously and without emotion that our efforts at learning and education are generally in the direction of doing complicated acts unconsciously

Unlike animals a large part of man's behavior is learned So far from it being true that human nature does not change human nature as compared with animal nature is remarkable for flexibility for plasticity and for its capacity to change Intelligent control of human nature doesn't concern merely thinking and skill in using skeletal muscles Education begins with learning control of the autonomic nervous system and plain muscle A pediatrician trains a baby when to get hungry The plain muscle of the alimentary tract is trained to go into action at stated times A baby of two or three months is trained to have one bowel movement a day at a specified hour The housebreaking even of a dog involves training of the autonomic system and it is worth thinking about in connection with the subject under discussion that a dog requires conformity to the proprieties of civilized living quite often without special training merely through an unguided learning of what plain muscle reactions the social situation calls for The civilized man learns emotional control learns to modulate blind fear into the forms of prudence caution and reverence learns to modulate blind rage into regard for justice and equity or in physiological terms the cortex requires guidance of the autonomic system The cortex is at once master and servant of the autonomic system It is servant in that the cortex must find ways to gratify the urges that come from the elder system It is master in that the only way of keeping order among competing urges is through guidance furnished by the cortex

These briefly are the fundamental presuppositions with which a medical man approaches the consideration of psychological problems though it must be admitted that his constant absorption in concrete situations involving less complex patterns of relationship tends to render

him distrustful of his footing in the more complex field of relationships of man with his fellows

A PLAN OF PROCEDURE

What Is To Be Done? If the considerations that have been brought forward are not to remain fruitlessly academic, they must result in a plan of action

(1) The futility of dealing with the problem of essential hypertension when the opportunity for studying the situation at the post mortem table is just around the corner has shown that we must transfer our attention to the beginnings. To look in the faces of a group of young people and realize that a fourth of them will die of hypertensive disease is a challenge to do something now. And yet at more medical schools no serious attempt to deal with hypertension as a life problem for each student has been made.

Can we tell who are probable hypertensives? Brown and Hines thought the Cold Pressor Test might serve to pick out potential cases of hypertensive reactors. Observation of large groups over a period of years would show whether this hypothesis is correct. The millions of youth in high schools and colleges form the clinical material to be studied. Ayman and Goldshine² recently have reported a much simpler technique for measuring hypertensive reactivity. This breathholding test is said to be more sensitive than the Cold Pressor Test and is to be preferred because it can be applied anywhere without the need of getting ice water and a suitable container for it. As a first step in studying the problem of essential hypertension, groups of thousands from different parts of the country might be cooperatively studied to show whether these tests actually mark out the potential hypertensives. If the suspicion that the tests are valid in this regard proves to be true, the task of studying hypertension would be greatly lightened. Of course a similar group who were known non-reactors would need to be observed for comparison. The material studied would be simultaneously grouped with respect to weight-height ratios with respect to family history, and perhaps other factors—climate, diet—should be included in the survey.

(2) Should it be disclosed as a result of these studies that hyper-reactors to the test are especially prone to develop essential hypertension it would probably also be shown that some hyperreactors never develop

hypertension and some who are not hyperreactors do develop it. Hyperreactivity would merely mean a special sensitiveness to certain classes of stimuli just as predisposition to acquiring allergic reaction (a case of cellular learning) might never develop allergy in an environment where stimuli were absent and just as a person with little predisposition to allergy might become allergic in an overwhelmingly allergic environment. By the means suggested a clinical material must be isolated that is in the early stages of essential hypertension and the selection of this material requires great care since it is by no means easy to determine what is a basal pressure, what are significant fluctuations, what changes are trivial and accidental. It cannot be supposed that the potential hypertensives will all manifestly emerge during school years. In order to study the problem successfully it will be necessary to continue observations on blood pressure throughout subsequent decades.

Such observations imply radical change in the attitude of medical men to their work and corresponding change in the attitude of patients to the need of medical care. It implies a general acceptance of the notion of preventive medical care. That such a shift of emphasis is by no means impossible is shown in the recent history of pediatrics. Prominent pediatricians say that 75 per cent of their income as physicians is derived from preventive pediatrics and are enthusiastic about the improvement in results obtained by this shift in approach to clinical material. Medicine has scarcely made a beginning in this obviously indicated direction but when such a beginning is made *there is no undertaking in preventive medicine that so readily lends itself to the continuous lifelong medical guidance as does the hypertension problem*.

(3) Such reorganizations of attack on the problem of hypertension can readily be effected. If there is promise of fruitful results such a rearrangement would soon be enthusiastically adopted. The nub of the question is: Can anything worth while be done when it is found that a young person is taking the path toward hypertension? If nothing can be done to divert the young person from progressive essential hypertension there is no use in discussing etiological factors, no use in merely plotting out a remorselessly inevitable course of events. It is the belief of the writer that when doctors come to apprehend the nature of the etiological factors, come to take a humanistic view of psychological relationships as closely analogous to physiological relationships of emotional

attitudes as something learned as habits that having been learned might be unlearned they will find effective means of intervening to redirect the formation of habits and attitudes that entail death as the outcome

(4) How shall we conceive effective means? Every physician has been faced with this question. Since ground for answering it has hardly been broken the physician shrinks from the practical difficulties which present themselves. The case may be that of a vigorous extrovert strenuously interested in getting ahead inherently resentful of any effort to impose restrictions on his attitude or way of life. The case may be one of a timid introvert where any suggestion of dangers ahead might lead to the development of morbid anxiety. The physician will ask himself. If this situation has developed through exposure to a general social attitude how can I alter the social climate?

The doctor-patient relationship generally demands that the patient should ask help of the doctor should feel the need of help and be willing to pay for it and that the relationship is awkward and unproductive of good if the doctor tries to force advice on those that have not sought it.

Further plans for dealing with arterial hypertension are like most therapeutic plans in that they mean sacrificing present good and enjoyment in behalf of future advantage. But it is hard to make a vigorous young person believe that he should derange his attitudes alter his way of life in respect of dangers that lie 30 or 40 years ahead a time that seems to him unimaginably remote. He is not readily interested in a doubtful project that offers to prolong his life 15 years after reaching what seems to him the advanced age of 58.

The difficulties which have just been presented could be greatly lessened in a group of people who are persuaded to submit themselves to the well warranted experiment of making their entire health concerns a matter of continuous guidance making the doctor-patient relationship not an outgrowth of the chance incidence of disabling sickness but a matter of confiding one's health affairs to an intelligent guide just as intelligent business men retain legal advice to keep from getting in trouble not merely to extricate them from trouble.

Even in the difficult individual situation outlined above a tactful approach may bring about intelligent cooperation between doctor and patient. Suppose that attitude of intelligent cooperation has been instituted what would be the next step? Obviously an inquiry into the

gaining control of the involuntary muscular action of the arteriole through a perfected control of the skeletal muscle as outlined by Jacobson in *Progressive Relaxation* will prove helpful for understanding. It may prove helpful to realize that the will to power as celebrated in success magazines and popular success psychologies constitute propaganda for emotional habits and attitudes which may in some instances be harmful and that the doctor himself may be a therapeutic agent of great value if he can successfully propagandize and institute a different habit the habit of equanimity of *Power through Repose*. (See Anna Payson Call's excellent popular book under this title.) While any emotion represents some break of smooth flow of feeling or action emotional attitude that leads to essential hypertension seems to be one in which a curb is placed on a strong need for action a sense of social urgency menaced by frustration. Hard labor doesn't produce hypertension but stress striving imply a need of action generated by social requirements but that has met with social obstacles.

The sphygmomanometer may sometimes have seemed to be a pretentious affair which has served to betray the natural piety that people feel for medical science. Yet it may be regarded as an instrument able to disclose in its beginning a type of physiological reaction that may lead to fatal consequences and still better it may be regarded as an instrument for the study of a psychological attitude which has been learned and as a means of telling us what progress we are making in our efforts to get a bad habit unlearned.

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patient's life history and emotional attitude. Is there an attitude of urgency menaced by frustration? This is a ticklish business, easily bungled. It involves subjecting to question cherished values; values which, though recognized by the physician as habits that have been learned, are identified by the patient with his very inmost self. If a doctor tries by explanation and persuasion to emphasize the value of calmness, steadiness, equanimity, imperturbability, it is pretty sure that better acquaintance with his patient will disclose a resistance to any alteration in certain concrete emotional attitudes.

These attitudes have risen in connection with ways of acting. The most natural way to alter them is through definite changes in the patient's activity, such as a different plan for spending one's twenty-four hours a day, a certain definite period to be given to deconcentration as a studied exercise. In some instances it may be necessary to undertake an investigation of the emotional attitude of a patient to certain persons with whom he is associated.

It must be remembered that emotion is directed toward persons, not lifeless objects. We speak of the sensation of hunger, sensation of pain from a blow, but of emotions, of anger, love, envy, pity toward persons. Even the sex urge may be just a feeling until by intermixture with many social and personal factors it becomes an emotion. The particular emotion to be dealt with may be one of shrinking, a lack of steadiness in grappling with the problems of daily life, or it may be an overwhelming love of power. In any case, a program of reeducation is apt to require expenditure of time and effort. Fortunately, there is a good deal of time available, since the development of hypertensive habits is usually slow and insidious.

(Discussion is omitted of the case of malignant hypertension, which is sometimes considered as a development of essential hypertension and may be, though it seems to present a different sort of problem, possibly related to infection.)

The gravity of the threat offered by essential hypertension will justify an alteration of occupation in an attempt to seek a calmer social environment. The threat justifies our using our wits in every way we can to get a better understanding of what is meant by habit and emotional attitude in the specific case before us. The study of habit as found in John Dewey's "Human Nature and Conduct," the study of the possibility of

gaining control of the involuntary muscular action of the arteriole through a perfected control of the skeletal muscle as outlined by Jacobson in 'Progressive Relaxation' will prove helpful for understanding. It may prove helpful to realize that the 'will to power' as celebrated in success magazines and popular success psychologies constitute propaganda for emotional habits and attitudes which may in some instances be baneful and that the doctor himself may be a therapeutic agent of great value if he can successfully propagandize and institute a different habit, the habit of equanimity, of Power through Repose. (See Anna Payson Call's excellent popular book under this title.) While any emotion represents some break of smooth flow of feeling or action emotional attitude that leads to essential hypertension seems to be one in which a curb is placed on a strong need for action, a sense of social urgency menaced by frustration. Hard labor doesn't produce hypertension, but stress striving imply a need of action generated by social requirements but that has met with social obstacles.

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CHAPTER XLIX

LOW ARTERIAL PRESSURE

By JOSEPH H. BARACH, M.D.

Historical: Herophilus¹ (570 B. C.) was the first to study pulse in health and disease. Galen² repeatedly declared that Hippocrates paid no attention to the character of the arterial pulse.

Corvisart failed to establish any relationship between peculiarities of the pulse and the heart, and Laennec stated that "exploration of the pulse is far from being able to give an idea of the general circulation."

Said Hope,³ in 1848: "During the past 41½ years, I have written notes on the pulse in 10,000 cases." One wonders what the good doctor wrote in those 10,000 observations, when it is considered how little has come down to us from the days before mechanical and recording devices. William Stokes⁴ said little that is impressive concerning arterial pressure and its clinical implications, and Sir William Broadbent⁵ wrote to his brother, in 1884: "I took for my subject, 'The Cause and Consequence of Undue Tension in the Arterial System,' a subject of immense importance in which I have led the profession. I had a packed audience and have had ample evidence since of the impression my address has made. It has already saved many lives."

Although Hales, in 1708, inserted a glass tube in a large artery to determine the height to which the blood would rise, thus measuring the *force within the vascular system*, most of the clinical knowledge of arterial pressure has been acquired during the more than 35 to 40 years since the advent of the mercurial manometer.

PRESENT STATUS

Today, just as the mercury column in the thermometer indicates normal, subnormal temperature, and fever, so does the mercury column in the sphygmomanometer indicate normal, low, and high arterial pressure. Regardless of the frequency with which either phase is met in health or disease, the total medical knowledge remains inadequate until all three phases are understood.

Values for normal pressure are now established and the significance of high arterial pressure is generally appreciated. There is today also a plenitude of clinical facts concerning low arterial pressure but what is still needed is correlation and evaluation of this knowledge. When that is fully accomplished it may be that a master key will be found and the cause of abnormal variations in health and disease will be uncovered. Once a basis for this functional abnormality is revealed many perplexing problems in medicine will be solved for physician and patient.

The proper placement of any phase or symptom in human disease is of really great importance. *If low arterial pressure is discussed as though it were a disease entity then the practitioner of medicine will treat it as such. Fortunately, this viewpoint never became established.* Arterial pressure variations should therefore be regarded either as evidences of altered physiological or as pathological functions.

Arterial pressure indicates the kinetic energy within the artery and it indicates relatively the pressure within the circulatory system. Low arterial pressure is a characteristic finding in certain types of apparently healthy individuals; it occurs under varying conditions of health and disease. Some clinicians believe that low arterial pressure does not occur in normal health.

Since up to the present time there is no final agreement concerning the etiology of low arterial pressure clinical analysis and synthesis goes on. That which is known seems to point to a definite underlying cause other wise how are the many unrelated diseases and abnormal conditions in which low pressure is found to be explained?

DEFINITION

Common experience among clinicians has led to consensus of opinion that a systolic pressure of 110 mm Hg or lower when found in the adult human may be regarded as low arterial pressure. While this is an arbitrary ruling valid objections have not been raised against it and 110 mm Hg is the generally accepted level at which low arterial pressure begins.

Diastolic pressure values have not come into the calculation because changes in its level seem comparatively insignificant. Pulse pressure changes in this as well as in many other conditions have likewise proved to be without well-defined clinical significance.

If the definition is accepted that health is the state of an organism in harmony with its surroundings and disease is the state of an organism in conflict with its environment in this instance a certain number of individuals will be found with low arterial pressure who seem normally adapted to the world in which they live. *In this sense, low arterial pressure exists both in health and disease.* There are men and women with low pressures who seem to live and work and play without disturbance of health. It is true that the clinician may discern certain evidences suggesting constitutional inferiority in these people but the individual may not be aware of inadequate health. If he thinks about it at all he considers himself as being of a different type with certain inherent physical limitations but aside from that he may feel well and under ordinary conditions he is well. The medical observer often wonders how such individuals work as efficiently and as ardently as many of them do.

The circulatory factors which determine low arterial pressure are presumably the same as those which are responsible for blood pressure as a whole. Physiology has defined arterial pressure as being dependent upon energy of the heart and resistance offered by the peripheral circulation. Total volume of the blood its physical properties and elasticity of the blood vessels are likewise important factors. From the standpoint of the clinician respiratory function and body movement should also be considered as forces of major importance.

PHYSIOLOGICAL CONSIDERATIONS

Adaptability of Forces in the Circulation One fact always to be kept in mind is that the circulation is maintained by three active forces of which the systolic pressure diastolic pressure and rate of the pulse are the outward manifestations. It is equally important to recognize that these three forces normally act in unison by reciprocating in each other. Thus it is when systolic pressure falls diastolic pressure and pulse rate tend to rise. When diastolic pressure rises systolic pressure automatically tends to recede and pulse rate slows. When both systolic and diastolic pressures rise the pulse rate tends to fall. This adjustment occurs in health and in disease every minute of the day and if for any reason this adjustment cannot be made strain and a breakdown sooner or later will follow. Thus it is that this triad is constantly at work and should be considered as inseparable values.

The purpose of this constant adjustment is of course the maintenance of cardiac output and blood flow throughout the 24 hours under all conditions and in response to the physiological needs of the organism. It is noteworthy that these changes are actually accomplished within a total variation of less than ten per cent. Thus the changing needs of the organism due to posture, digestion, respiration, chemical and nervous stimuli are met to maintain a constant physiologic equilibrium of the organism.

The blood pressure readings record these variations. The patient who has somehow learned the level of his blood pressure and insists on knowing what the findings are, may fail to understand the meaning of this physiological variation and may come to look upon the whole procedure with askance. A well known columnist of the day told the story of his visit to a doctor in the morning who told him that the source of his symptoms was low blood pressure. This worried him so much that later in the day he sought another physician who, after taking his blood pressure, said to him, "The trouble with you is that your blood pressure is too high." Whereupon the poor man cried unto himself, "A plague on both your houses," and on the following day filled a newspaper column with his opinions about patients, doctors and blood pressure readings. What to him was a demoralizing jigsaw puzzle had the elements of truth, but these truths were not put together for him in an understandable way. He should have been told that his nervousness and his anxiety, or any other physiological adaptation, will produce such variations in blood pressure in one day and that it is nature's business to do so or else he would soon be in trouble.

It is a cause for criticism in clinical medicine that systolic and diastolic pressure readings are not always accompanied by a statement of the pulse rate, without which a complete interpretation cannot be made. Not only for diagnosis but for prognosis as well, does the pulse rate give additional information. Personal experience has proved that the rate of the pulse is one of the most valuable factors upon which to base a prognosis in high arterial pressure.

The Energy Index. In present-day conceptions of the dynamics of the circulation, clinicians think in terms of an efficient circulation where all the factors are within the normal range. They think of high arterial pressure as a state of overwork and strain of the circulatory apparatus.

and of low arterial pressure as a state of circulatory inefficiency accompanied by various circulatory and systemic disturbances.

Since blood pressure readings are evaluated in measurable and quantitative values, it would seem advantageous to be able to express the findings in quantitative terms. A systolic pressure reading of 220 mm. Hg has a definite meaning in clinical medicine, and a diastolic pressure of 120 mm. Hg is likewise significant. Equally so is a pulse rate of 120 as contrasted with a rate of 80 beats per minute. The clinician of today accepts these values without question and is guided by them in his interpretation of disease. When all is said and done, these are commonly

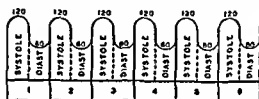


FIGURE 1 Graphic representation of 6 pulse beats each beat consisting of a force of 200 mm. Hg

accepted values in his daily work. Along with these, various formulas have been proposed from time to time for measurement of the pulse pressure-pulse rate ratios, as well as pulse pressure ratio to systolic pressure, diastolic pressure and pulse rate. From such calculations, attempts have been made in the past to calculate velocity of the blood flow, work of the heart, and circulatory efficiency. *Up to this time, it may be said that these abstract calculations have produced little that is of permanent value, and that today, there is not yet a formula which truly indicates the work accomplished nor the efficiency of the circulatory apparatus.*

There is a method of calculation, first described in 1911 as the Energy Index,^{7, 8, 9} which may be considered here, and one which does have a certain value in this connection. The energy index is based on the three values which are of admitted clinical significance: The systolic and diastolic pressures and the pulse rate. If in a given case, the lifting force of the systolic phase of the heartbeat is 120 mm. Hg and the diastolic force is 80 mm. Hg, then the force behind the entire pulse beat is represented by 200 mm. Hg (Fig 1).

When there are 72 pulse beats, comprising 72 systoles and diastoles, then the force for the whole minute is $72 \times 200 = 14,400$ mm. Hg. This

14 400 mm Hg pressure is an index of the energy expended by the circulatory system it is not a measurement of the total force. An extensive application of this formula to average healthy individuals⁹ revealed that the normal energy index will be found to be not over 20 000 per minute. This formula indicates—it does not measure—the total expenditure of energy by the cardiovascular system.

When this formula is applied to readings in a case of high arterial pressure the result is as follows:

$$\begin{aligned} \text{Systolic pressure } 180 + \text{Diastolic pressure } 110 &= 290 \\ \text{Pulse rate } 90 \times 290 &= 26\,100 \text{ total} \end{aligned}$$

In a case of low arterial pressure the following will be found:

$$\begin{aligned} \text{Systolic pressure } 98 + \text{Diastolic pressure } 64 &= 162 \\ \text{Pulse rate } 80 \times 162 &= 12\,960 \text{ total} \end{aligned}$$

Thus the relative energy expenditure of the cardiovascular system is contrasted in a case of low arterial pressure which is 12 960 with a case of high arterial pressure which is 26 100 mm Hg per minute.

A high index means increased cardiovascular effort. Either the action of the heart and blood vessels is accelerated because of inability to accomplish their work at a normal rate of activity or they are fully capable of doing their work but the resistance to their functioning is great. In either case a greater than normal amount of energy is expended and with this there is an accompanying increased wear and tear on the circulatory apparatus.

A low index means either that the circulation is accomplished with little expenditure and waste of energy or there is an inability to expend the necessary effort because of physiologic alteration and disease. Naturally a slow pulse rate means a longer period of diastole and a longer rest period between each systole.

Low arterial pressure is a clinical phenomenon characterized by a low energy index of the circulatory system. A lower energy expenditure so long as it is not the failing energy induced by disease is indeed a conservation that is beneficent. As will be seen in the discussion on prognosis these patients actually carry on for a longer time than those whose circulatory system is more responsive to the stimuli of the day but with greater wear and tear and more ultimate damage.

ETIOLOGY

The impelling question that arises at this point is this Why is it that in two human beings living under exactly the same conditions subjected to the same atmospheric pressure of 15 lbs per square inch on all sides, controlled by the same chemical and biophysical forces, one is found with an arterial systolic pressure of 200 mm Hg and the other carries a pressure of only 100 mm Hg? Is this fact in any way comparable to the working of a high pressure and low pressure engine in the field of mechanics and physics? Is the explanation to be found in something like the ratios of narrow bore and long stroke of the high pressure engine as compared to the wide bore and shorter stroke of the low pressure

<i>Gasoline Engine</i>	<i>Comparable to</i>	<i>Cardiovascular System</i>
Narrow bore + long stroke = high compression	comparable to vasoconstriction	-- high arterial pressure
Wide bore + shorter stroke = low compression	comparable to vasodilatation	low arterial pressure
Gasoline + normal air and oxygen = normal power	comparable to glucose + oxygen	-- normal energy
Gasoline + air and more oxygen = greater power	comparable to glucose + more oxygen	= more energy
Gasoline + less oxygen = reduced power	comparable to glucose + less oxygen	= less energy
Gasoline + ethyl + oxygen = maximum power	comparable to glucose + hormone + oxygen	= maximum energy

engine? Is it perhaps in the character and quality of the fuel or the air oxygen mixture? Or after all, will the complete answer be found in the type of engine plus the quality of the fuel plus the amount of available oxygen? This analogy may seem very crude until we review the available facts concerning low arterial pressure and then we suddenly realize the counterpart in each of these two mechanisms and their similarity, as will be seen in the latter part of this discussion

INCIDENCE

In Health The incidence of low arterial pressure in groups of healthy people shows a surprising constancy Extensive observations reveal the fact that in a cross section of population at the ages of 17 to 30 the incidence of low arterial pressure was found to be about 3.5 per cent, varying within the limits of 1.8 to 6 per cent¹⁰ These values have been obtained in students, army recruits and similar groups They are there

fore assumed to be true for the general population at those ages. On the other hand a group of apparently healthy bank clerks at similar ages coming out of the same general population showed a striking difference. In this special group 38 per cent of males and 55 per cent of females had a blood pressure of 110 mm Hg or less.

This is most interesting. One explanation is that the individual with a constitutional tendency to low arterial pressure unable or unwilling to cope with the rugged issues of life desires seclusion and protection knowing that these conditions can be obtained within the walls of the counting house he or she gravitates to such an occupation. Once there

TABLE I
INCIDENCE OF LOW ARTERIAL PRESSURE IN VARIOUS GROUPS

<i>Class</i>	<i>Number Examined</i>	<i>Arterial Pressure 110 or Less</i>	<i>Incidence Per Cent</i>	<i>Editor</i>
Students male	656	30 cases	4.0	Barach and Marks
Students female	1100	24 cases	2.1	Barach and Marks
Recruits (31 596) male	1315	73 cases	5.6	Barach
Recruits (27 224) female	1016	24 cases	2.3	Barach
Aviators male	1000	18 cases	1.8	Harris
Students female	6000	132 cases	2.2	Alvarez
Bank clerks male	108	41 cases	38.0	Barach
Bank clerks female	169	94 cases	55.0	Barach

the limited space in which they spend the day limitation of muscular and respiratory movement added to an already existing tendency produce the final striking result.

Of course the level of 110 mm Hg or less has been arbitrarily chosen as the beginning of low arterial pressure. We have accepted that level here largely because of usage by the medical profession as a whole in order that we may all be speaking in the same terms and to avoid confusion. There is much justification in saying that since a level of 110 mm Hg is compatible with apparent good health we should adopt 100 mm Hg as the level of low pressure but this would throw out of consideration a great deal of work and data that has been accumulated over the past 40 years. The clinician is well aware of the element of relativity here and allows for this in his interpretation and evaluation of the patient and his disease.

In Disease In a previously healthy individual when low arterial pressure is brought on by disease it is assumed to be due to the cardiovascular depressant action of that disease. In an individual bordering on low arterial pressure the cause may even be a minor one.

The following tabulation suggests the various physiological and pathological states in which low arterial pressure is encountered and the conditions which tend to produce it.

In Health

Infancy	Body build
Childhood	Exercise
Adult constitutional type	Posture
Racial tendency	Respiratory system
Geographic location	Heart
Climate	Blood vessels capillaries
Atmospheric conditions	Autonomic nervous system
Body weight	

In Disease

Constitutional diatheses	Physical and nervous exhaustion
Disorders of respiratory system	Shock
Disorders of heart	Medical
Disorders of blood vessels	Surgical
Disorders of blood	Acute infectious diseases
Chemical	Chronic infections
Physical	Focal
Morphological	Tuberculous
Endocrine system	Syphilis
Disorders of nutrition	Acute intoxications
Diabetes	Chemical agents
Deficiencies	Food poisoning
Cachexias	Drugs

CLINICAL GROUPING OF CASES

In a recent group of 186, ambulatory general medical cases in private practice 253 showed low arterial pressure. This is about four times as many as would be found in a similar sized group of well people as our previous findings indicated.

Some allowance must be made for the accompanying classification of these cases. Individual experience and diagnostic acumen might lead one worker to place a case in one group while another might place the same

patient in one of the other groups. This is particularly true of the constitutional, endocrine and focal infection type of case.

In the reports of various writers on this subject it is clear that associated disease incidence varies with geographic location in which the observations were made, whether the patients were ambulatory or hospitalized and the type of case likely to consult the physician who made the reports.

TABLE II
253 CASES OF LOW ARTERIAL PRESSURE

<i>Clinical Classification</i>	<i>Cases</i>
Constitutional types including asthenics	81
Endocrine types	60
Chronic infections known localizations	49
Constitutional types with marked gastro intestinal symptoms	79
Blood dyscrasias	11
Bronchial asthma	9
Cardiovascular renal disease	8
Carcinoma	4
Lues secondary	1
Psoriasis	1

SYMPTOMS

The symptoms in patients classified as low arterial pressure vary with the intelligence and psychologic background of the individual. A list of the patients' complaints may be as unreal as answers to a questionnaire. In some instances the patient becomes an artist for the time being painting a picture for the doctor's benefit. Some of these pictures are drab and foggy while others are done in gorgeous and flamboyant colors. The physician on guard will separate the wheat from the chaff and give heed only to those symptoms which have true clinical significance.

The 35 per cent of humanity with essential low pressure are of course in the front line of attack. When unfavorable conditions arise they will be the first to show symptoms. Whatever the strain after it is set in full motion symptoms appear which may manifest themselves in any organ or system of organs in the body. The symptoms may be localized or general. The commonest of all complaints is loss of their former sense of well being, and this is accompanied by early fatigue and physical exhaustion. At times they have dizziness and motor instability. Symptoms referable to the mental and nervous systems are apprehension, fears,

nervousness insomnia inability to concentrate often on anything but themselves inattention and headache Some complain of tinnitus aurium and neuralgic pains others have intermittent abdominal pains they complain of arms and legs going to sleep and paresthesias

Precordial pains at times indistinguishable from true anginal pains are a source of anxiety to patient and doctor They are apt to come on after the patient has done more than he should after taxation by physical or mental strain after overeating drinking smoking constipation or any other stress It is stress and strain of any kind that these patients cannot tolerate

Frequently this is the type of patient who says he is at his best toward evening when the normal man and woman begins to notice the fatigue of the day These patients will go out to dinner where they are likely to overeat and smoke and take liquor and gather a good deal of momentum in the course of the evening By bedtime they are wide awake and when they finally do get to bed they are apt to be sleepless for two or three hours If they do fall asleep they are apt to awaken at 3 or 4 A M and remain wide awake These patients are sensitive to coffee and to tobacco Often they become addicted to the use of sedatives and somnifacients which leave them with mental depression and in a daze the following morning In some instances the patient experiences marked unsteadiness of gait after the use of such drugs In most instances more harm than good comes from their use Some have spastic constipation for which they take laxatives of one kind or another daily and this hypercatharsis may also be a cause of dizziness or giddiness to the point of disturbed locomotion In the morning the rested individual is ready for a day's work but the patient with low arterial pressure is only too often jaded and unfit for the coming day Thus a vicious cycle is established which keeps them in a state of misery and semi invalidism from which many cannot extricate themselves

It should be remembered that these patients are not continuously in this low state They have periods of well being which alternate with periods of depression During the depressed states the blood pressure reaches its lowest levels Whether a temporary fall in pressure is the cause of the entire episode or is only a part of it is not so easily determined that they do occur simultaneously is a common observation

Referable to the cardiovascular system are precordial pains, dizziness, palpitation, faintness, and syncope. Referable to the digestive system are indigestion, abdominal discomfort from "gas" in the stomach or intestines, spasticity, and mucous colitis with its accompanying symptoms. Such are the usual complaints of the patient with low arterial pressure

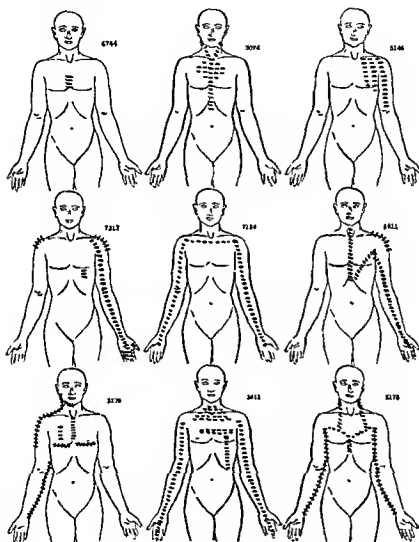


FIGURE 2 True cardiac pain areas

The subject of precordial pains, or the "heart pains," of these patients deserves special consideration. While it is often necessary to encourage them and allay their fears, there are times when the doctor is not as sure of himself as he would like to be, in telling the patient that his chest

pains are not of cardiac origin. Not infrequently pains occur over the right chest as the counterpart of heart pains over the left precordial area and this is welcomed by patient and doctor as evidence that the same kind of pain over the heart area is not necessarily of cardiac origin.

Many years ago the writer began charting carefully the chest pains precordial and others in a series of organic cardiovascular cases. This study included arterial hypertension diseases of the heart, aorta and of the

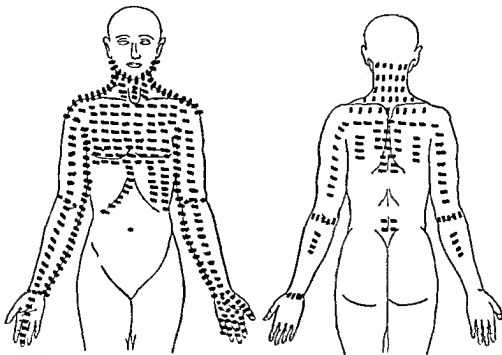


FIGURE 3 Composite picture of cardiac pains

coronary vessels. As will be seen in the accompanying illustration (Fig. 2), there is hardly an area over the upper half of the body which may not be affected by these pains. It was not long after this study was undertaken that a composite chart of these pain areas (Fig. 3) was found to cover the entire body outline, front and back, a convincing evidence that referred surface pains in true cardiovascular disease have a wide and varied distribution.

In the light of these studies and similar observations in the so-called functional cases and in patients with low arterial pressure one should not deny too positively the meaning and import of these recurring pains. In fact, clinical experience has taught that the chest pains of neurotic

patients should be studied just as carefully as other patients, because some of them will surely end up with coronary occlusions or cardiovascular failure.

LOW ARTERIAL PRESSURE FROM THE STANDPOINT OF THE HUMAN CONSTITUTION

Without a systematic grouping of the facts, the entire subject of low arterial pressure is a confused mass of disconnected observations leading nowhere. It is in good order, therefore, to subdivide and arrange the available data in such a way that it will have more meaning and lead toward a better understanding. For this, the panel arrangement of Draper,¹¹ as applied in the study of the "Human Constitution," serves admirably.

1. Anatomical and Pathoanatomical Panel: (a) *Age*: Infancy to old age is accompanied by a gradual rise in arterial pressure. Observations indicate that pressure levels tend to change at the epochal periods of life; puberty, maturity and menopause.

(b) *Sex*: From puberty onward, when comparable groups are studied, arterial pressure is found lower in the female than in the male. It is also true that the woman with disease involving her sex organs, will frequently have higher arterial pressure than the woman with normal organs and sex characters. This was observed by Barach,¹⁰ Alvarez,¹² and others.

(c) *Body Weight and Body Build*: Most individuals with low arterial pressure are underweight. Reports of medical examiners for life insurance and those of many other observers indicate that this is a general rule.

Our observations on 129 cases of low arterial pressure reveal that the body weight of these individuals as compared to the normal standards for age, height and weight, was decidedly lower than the average normals. Of these 129 cases, 105 were underweight, varying from 2 to 56 lbs. Twenty-two were overweight, varying from 4 to 82 lbs. and two were of normal average weight. Thus 81 per cent of our cases were underweight and 17 per cent were overweight.

It is not an uncommon experience to find a systolic pressure of 90 mm. Hg in a man 6 feet, 3 inches in height. Underweight may be said to be a characteristic of the *typus hyposthenicus*;¹⁰ and no doubt undernutrition, as in the case of the bank clerk, is a contributory factor in the persistently low arterial pressure case.



FIGURE 4 Hyposthenic type, hypotension 68 per cent (Barach Arch Int Med)



FIGURE 5 Sthenic type hypotension 97 per cent (Barach Arch Int Med)



FIGURE 6 Hypersthenic type (Barach Arch Int. Med)

Well proportioned women show a blood pressure average of 10 mm Hg higher than thin women.¹³ On the other hand there is a group of endocrine females with low arterial pressure who frequently are overweight.

By classifying individuals as hyposthenic, sthenic and hypersthenic it was found that those with low arterial pressures definitely belong to the hyposthenic type. Occasionally an individual of the hypersthenic type is found with low arterial pressure but they are the exceptions. Mistaking the obese for the hypersthenic must be guarded against. A normal chest may be so covered with layers and pads of fat that it has the outward appearance of the hypersthenic whereas in the latter it is the bony

TABLE III
PULSE RATE IN 140 CASES OF LOW ARTERIAL PRESSURE

Number Cases	Pulse Rate
34	90 to 110
54	80 to 90
52	60 to 80

framework of the thorax and its wide and deep contour which produce the characteristic chestiness.

(d) *Respiratory System*—The respiratory system in the hyposthenic of the constitutional type shows a state of development in keeping with the shape of the thorax. The reduced vital capacity of these individuals indicates that the respiratory function is of a lower order of efficiency. Uncomplicated asthma particularly in younger patients is frequently accompanied by low arterial pressure. It is also in order here to mention the fact that in patients with dyspnea on exertion and cardiac decompensation vital capacity is lower than normal. Where there is both diminished vital capacity and a failing heart low or a falling arterial pressure is the rule.

(e) *Cardiovascular System—Heart*—There are more normal or slow pulse rates than fast ones in individuals with low arterial pressure (Table 3).

Physical examination and x-ray studies reveal the fact that the constitutional types with low pressure have a narrower and longer heart

than the normal. The gourd shaped heart is part of the slender build of the hyposthenic. It is the type of heart found with enteroptosis in the tuberculous and not infrequently in the coal miner with silicosis. In cases of low or falling arterial pressures other than that of the constitutional type integrity and functional capacity of the heart and blood vessels determine the level to which arterial pressure descends. Where the myocardium or aorta is diseased low arterial pressure should make one apprehensive of a possible sudden fatality.

Vascular System. The normal or abnormal artery, capillary or vein and the degree of fibrosis in the vessel determines its elasticity, distensibility and contractility. All are important factors in determining arterial pressure level. It should be recalled here that only half the cases of arteriosclerosis show high arterial pressure and that in arteriosclerosis without high arterial pressure or where the arterial pressure is low the work of the ventricle is not increased.¹⁴

2 Physiological and Pathophysiological Panel (a) Respiratory System. There are many relations between respiratory function and arterial pressure. As already suggested in the preceding paragraphs it is inevitable that the underdeveloped and hyposthenic thorax should produce deficient functioning of the respiratory system. Diminished oxygen supply, whether it is brought about in ascending high altitudes, whether it is produced in a closed chamber with gradual reduction of oxygen or replacement of the normal amount of oxygen by carbon dioxide, carbon monoxide¹⁵ or any other gas, whatever be the mode of producing anoxemia, fall of arterial pressure is the inevitable result. There are of course innumerable ways of producing anoxemia. It may be the result of alterations in the environment or in the living being itself; it may be exogenous or endogenous in origin. Thus any function or any organ of the body may directly or indirectly take part in production of low arterial pressure.

(b) Oxygen and Capillary Circulation. Experimental evidence concerning the part played by oxygen as a cause of capillary contraction and the part played by anoxemia in producing dilatation is too voluminous to quote. The work of Meyer in 1906 and of Rothlin in 1920 has been repeated and substantiated by many physiologists.

Rothlin¹⁷ has shown that in Ringer's solution without added oxygen the isolated vessel is completely relaxed while in Ringer's solution

through which oxygen is being passed, the vessel attains irritability and contracts directly in proportion to the amount of available oxygen. This contraction phase happens even after a relatively long latent period.

Oxygen effect occurs irrespective of nervous influences responsible for vasoconstriction and dilatation, and irrespective of other chemical or biochemical vasoconstricting substances in the blood.

Thus it is that anoxia is a factor in shock. Low oxygen supply, paralysis of capillaries, diminished blood flow, falling blood pressure; which, after reaching a systolic level of 80, because inadequate to carry on the circulation and after that, the manifestations of shock appear.

Of great significance in this connection is the work of the staff of the United States Bureau of Mines at Pittsburgh in their studies on respiratory anoxemia.¹⁵

Chornyak and Sayers¹⁸ found that when inspired air is poor in oxygen, or in asphyxia, altered circulation, particularly vascular dilatation and stasis invariably follow. When asphyxia is induced by carbon monoxide, there is actual edema of the dorsal motor nucleus of the vagus and adjacent areas in the medulla oblongata and consequent respiratory failure. Taken as a whole, their findings clearly indicate that inefficient respiratory function and insufficient oxidation lead to dilatation of the capillaries. Dilatation leads to fall in capillary and vascular pressure and then to low arterial pressure. Accumulating evidences, both in the clinic and laboratory, thus point to a direct relationship between oxygen, anoxemia, capillary dilatation, and low arterial pressure. Many years ago, Greene and Gilbert¹⁹ showed that low oxygen tension causes a depression of cardiac function.

Lavoisier's discoveries proved that oxygen is the essential element in respiration and, therefore, of life and that without oxygen everything must stop. Today, it may well be asked, what motivates oxygen? The chemist and biophysicist are again working in a new field. They are studying the oxidation reduction potentials, the factor which makes oxygen available. Perhaps this will bring new clues to bear on some difficult problems.

Atmospheric pressure changes and heat have their effect on arterial pressure.²⁰

(c) *Heart*: Physiological disturbances of the heart, the arrhythmias *per se*, cause slight or transient lowering of pressure. Their effect on

arterial pressure is proportionate to duration and severity of the irregularity. The accompanying myocardial factor in these cases is of greater importance. Pulsus alternans with low arterial pressure indicates grave myocardial damage.

(d) *Nervous System* The autonomic nervous system is a factor in low arterial pressure. It is governed by certain higher centers and in turn it controls various functions along the lines of its distribution. The studies of Ellis and Haynes²¹ point to the brain as a probable center of control. Of the parasympathetic and sympathetic systems the latter is probably more important influencing blood pressure through its excitatory and inhibitory effects on glands of internal secretion.

(e) *Shock* This need not be discussed here other than to mention that blood pressure reaches its lowest level in shock and in syncope. In shock the fall in pressure comes suddenly, whether its cause is biochemical, physical or psychic (See Chapter XLVI).

(f) *Blood—Anemia* Anemia may be accompanied by low arterial pressure both happening in the same patient. Whether it be acute anemia due to sudden loss of blood or chronic anemia from protracted bleeding or slow blood destruction the arterial pressure level is found at times to correspond to the blood picture.

Pernicious Anemia In a group of 25 cases three patients showed low arterial pressure during the period of observation, i. e. from the time of the first visit to the time of recovery under liver treatment. In fatal cases low pressure would be expected in the late stages of the disease but low arterial pressure is not part of the clinical picture of this disease. Finding only three cases of low arterial pressure in 25 patients with pernicious anemia would seem to be in keeping with the observations of Draper who finds by actual measurements that the thorax of the patient with pernicious anemia is deep and wide, the opposite of the hyposthenic type. No doubt other important factors enter into the level of blood pressure in these cases, one being the enlarged heart of pernicious anemia.

A study of the blood in a group of 139 cases of low arterial pressure reveals that 78 per cent of this series had less than 5,000,000 red cells, that 50 per cent showed hemoglobin under 70 per cent and that 89 per cent showed a polynuclear count varying between 50 and 70 per cent and only 8 per cent had a polynuclear count of 75 per cent or over. This blood picture serves as an index to the quality of the patient's tissues. We

have in this suggestions of secondary anemia and a low polynuclear count which is consonant with the general appearance and state of health of these patients

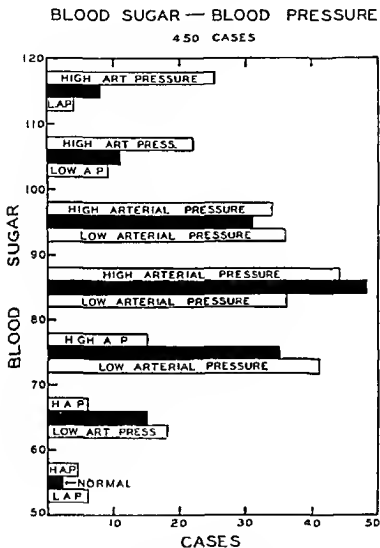


FIGURE 7 Blood sugar and blood pressure—450 cases

(g) *Blood Sugar* In 1934 the writer²² called attention to the observation that patients with low arterial pressure have a lower than normal blood sugar. Continued studies have verified these findings and have added to the significance of this observation in patients with low arterial pressure. It was first pointed out that in 24 out of 27 patients the blood sugar was under 110 mg $3\frac{1}{2}$ hours after breakfast. The present

studies include a series of 150 cases of low arterial pressure and a similar number of cases with normal and high arterial pressure. As chart (Fig. 7) clearly shows, the low pressure groups were the ones in which the lowest

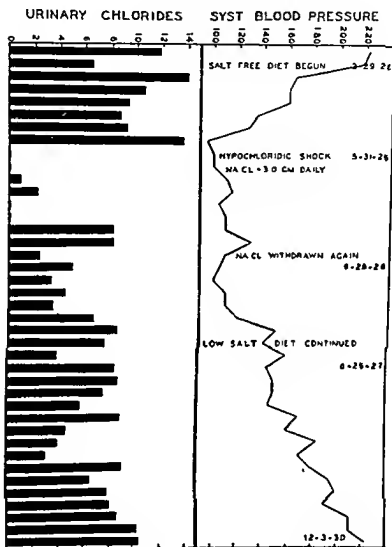


FIGURE 8 Effects of a "salt free" diet on blood pressure and urinary chlorides

blood sugars were found, and as the blood sugar reached higher levels, the arterial pressures were found to be at the normal or above normal levels.

In our recent compilation of a group of 30 selected cases of renal glycosuria in which the blood sugar is invariably lower than normal, it is

likewise revealed that the uncomplicated cases showed low arterial pressure

In this connection it is of additional interest to note that low arterial pressure is a characteristic of the Chinese people in whom diabetes is comparatively rare and usually mild

Thus we have in these various findings the association of low arterial pressure and low blood sugar

(li) *Chloride Metabolism* To what extent is the chloride metabolism involved in arterial pressure? Numerous studies have been made of the chloride metabolism in hypertension and for many years the salt free or low salt diet was considered an inherent part of the proper treatment of the hypertensive patient. *Looking back on the entire experience at the present time, it must be admitted that in most cases little of real therapeutic worth has been added to the patient's well being by a strict salt control.* Nevertheless the elimination of salt from the diet certainly does produce a physiological effect. While it may not be said that striking effects are seen in all cases yet it must be noted that in some the circulatory and systemic effects are very pronounced

An example of this is to be seen in the following case. Ralph McC aged 46 suffered with hypertension and nephritis. He was one of a group of patients under observation for a period of five years during which time we studied the blood and urine chlorides continuously and their relationship to blood pressure. As shown in Fig 8 there was a time in the evolution of this patient's disease in which his chloride metabolism was involved and control of the chloride intake was followed by marked circulatory and systemic effects

On March 3rd he was placed on a normal protein moderate fat diet and sufficient carbohydrate to meet his caloric requirements. With this he was given a salt free diet which means that no salt whatever was added in the cooking since a completely sodium chloride free diet is almost impossible. As will be seen in the chart by May 31st the chlorides had disappeared completely from the urine and his blood chloride had diminished from 520 mg to 280 mg. By that time his blood pressure had dropped from systolic 222 to systolic 100 mm Hg. With this salt disappearance and fall in blood pressure he developed clinical symptoms of a state of shock which were alarming. Profuse sweats coldness of the extremities dizziness and inability to sit up were noted. Sitting on the edge of the bed caused him to slide off to the floor and attempting to stand and walk resulted in a fall. To relieve these distressing symptoms he was given 3 Gm of salt daily which was promptly followed by disappearance

of his distressing symptoms. As the chart shows within three weeks a normal chloride output was reestablished with simultaneous clinical improvement. After that on a measured low salt diet we were able to maintain him at a 4 to 8 Gm salt output daily and in a state of normal well being.

In the course of the following five years his pressure gradually rose as part of the evolution of his disease until he finally died with various peripheral vascular lesions including retinal hemorrhages renal hemorrhages and finally cerebral hemorrhage. Here then is a case in which a too strict elimination of salt from the diet converted a case of high arterial pressure to one of low arterial pressure with its accompanying clinical disturbances and symptoms.

(i) *Endocrines*—What relationship if any do we find between the low arterial pressure phase and the endocrine phase in these patients and are they interdependent or are they merely coincidental? A review of the cases in this series of 253 patients with low arterial pressure which are classified as belonging to the endocrine group reveals some interesting findings. First of all 61 per cent of the endocrine series were clinical cases of gonadal disturbance or gonadal insufficiency. Here we found young people with obesity such as is generally designated as pituitary disturbance. There were cases of cryptorchidism abnormalities in the external sex characters and there were clear cut cases of functional hypogonadism indicated by sex infantilism in the male and various evidences of hypoovarianism in the female. Hypothyroidism following thyroidectomy and cases diagnosed hypoadrenia were also present in the group.

Hippin and Smith²³ recently reported seven cases of Addison's disease in negroes in addition to seven cases previously reported by others. Eleven of these came to autopsy and all of them revealed tuberculosis of the adrenal glands. All the cases in which the level of blood pressure was recorded had low arterial pressure of a marked degree.

Since the clinical syndrome of the various endocrine disturbances are in many cases multiple in character representing not an individual glandular disturbance it is just as well at this stage of our knowledge to consider them as composite examples rather than instances of specific gland disturbances.

(j) *Other Physiological and Pathophysiological Functions*—Exertion, fatigue and physical exhaustion have their influence upon arterial pres-

sure Every individual, quiet or resting, attains a basal level which is normal for him There is a diurnal variation as well During muscular effort, blood pressures rise in proportion to severity and duration of the effort and the fitness of the individual This rise continues for a variable period and is followed by recession to a subnormal level, which continues for a time As restitution occurs the blood pressure again rises to normal

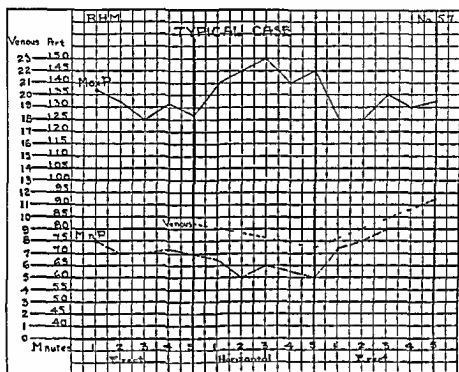


FIGURE 9 Chart showing maximum and minimum pulse pressure in the erect and horizontal positions in a typical case (Barach and Marks Arch Int Med)

This chart shows the effect of change of posture on the systolic (max.) and diastolic (min) pressures. It will be noted that while in the erect posture, the systolic and diastolic pressures were at an even level. When the horizontal posture was assumed the systolic pressure rose and diastolic pressure fell. After five minutes when the erect posture was again assumed the systolic pressure fell and diastolic pressure went up. The venous pressure as indicated by the broken line follows the level of the diastolic rather than the systolic pressure as is to be expected.

(k) *Posture*—Change of posture is accompanied by alteration in systolic and diastolic pressure and pulse rate.²⁴ These adjust themselves in a short time. Those with poor musculature and low vasomotor tone do not respond as promptly nor in the same way as those who are physically fit. A healthy man put to bed will have a fall in arterial pressure which will return to normal as he resumes his normal activity.

(l) *Orthostatic or Postural Hypotension*—This has been described as a clinical syndrome in about 20 cases during the past few years, although it was first delineated by Bradbury and Eggleston²⁵ in 1925. Time will tell whether this condition really deserves to be considered as a clinical entity and whether postural hypotension will find a place in the nosography of medicine.

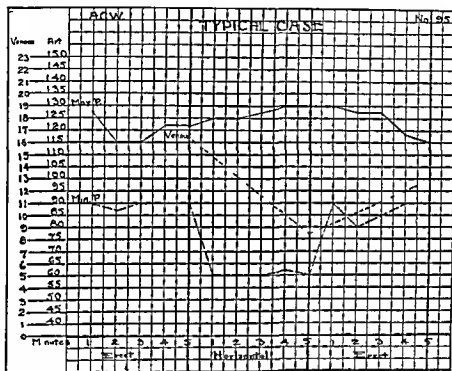


FIGURE 10 Chart showing maximum and minimum pulse pressure in the erect and horizontal positions in another typical case (Barach and Marks Arch Int Med)

As reports on these cases make their appearance in medical literature the clinical components of this syndrome are described as (1) a fall of systolic pressure to the point of syncope when the patient assumes the erect posture, the patient being comfortable in the horizontal posture only, (2) an inability to sweat and greater discomfort during the summer months, (3) slow and unchanging pulse rate with change from horizontal to erect posture, (4) low basal metabolic rate, (5) high blood urea and nocturnal polyuria, (6) evidences of pathology in the central nervous system and apotenia.

The pathologic physiology of this condition appears to be a failure of the sympathetic nervous system which normally controls vasoconstriction, acceleration of the pulse, sweating glands etc.²¹ Of special interest to the writer is the nocturnal polyuria which was almost invariably present in the reported cases. Clinical studies have shown that while nocturnal polyuria is ordinarily found in the hypertensive nephritic group of cases, it also occurs in patients with low arterial pressure.²² Those

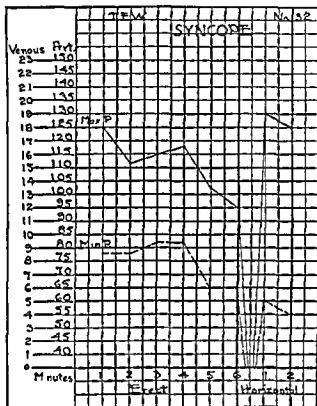


FIGURE 11. Chart showing rapid fall in pulse pressure during the experiment with syncope in six minutes. Rapid rise on placing the patient in a horizontal position. (Barach and Marks Arch Int Med)

studies revealed that the causative factor in nocturnal polyuria was circulatory and that it was induced by slowing of the pulse, prolongation of the diastolic phase and alteration in the pulse pressure during the hours of sleep, all of which led to the filtration of more water through the kidneys. Urea and chlorides in the blood content and urinary output revealed no constancy in either direction.

In the cases of orthostatic or postural hypotension studied and treated thus far, as reported by the various writers,^{27, 28, 29, 30} best results were

obtained by the use of ephedrine sulfate, benzedrine sulfate and neosyn ephrine hydrochloride. Of these, the latter seems to have been most effective.

(m) *Sleep*—There is a distinct fall of 10 to 12 mm Hg arterial pressure after the fourth hour of sleep just as there is in the pulse, respiratory and metabolic rates. During sleep muscular movement, circulation and oxidation find their lowest levels of the day. A very telling observation is recorded in a recent book by Agnes Smedley, 'China Fights Back'. As war correspondent with the 'Eighth Route Army', in the Japanese invasion of China in 1937-38 she relates some facts concerning the Chinese people as she saw them in large numbers.

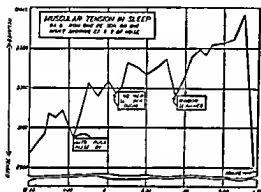


Fig. 12

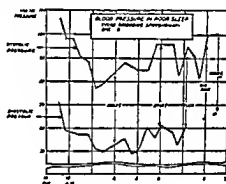


Fig. 13

FIGURE 12 The subject did not wake up during the night but his muscles were aroused by the external noises. It may have been dreams that caused the other increases in his muscular tension from time to time. (Laird and Muller Sleep, John Day & Co. Inc.)

FIGURE 13 The night on which this test was made was hot and noisy. Notice the sudden rises in blood pressure during the course of the night. The upper curve is for systolic blood pressure, the lower curve for diastolic pressure. Both curves are for the same sleeper. Notice what the noise of the truck and milkman did. (Laird and Muller Sleep, John Day & Co. Inc.)

I then lay awake watching the dark forms of the men about me. They lay without moving, hour upon hour. This interested me. I think most people tumble in their sleep. The Chinese peasants and workers lie for hours quiet and unmoving. I think that some of them do not turn over all night long. I have slept side by side with them many nights and I have not seen them move.

In contrast to this observation concerning the Chinese, kymographic studies made on a group of young Americans at Colgate University³¹ revealed that the average male subject moved sufficiently in his sleep to jar the bed six times per hour and the average female moved 30 per

cent less. With this degree of muscular activity, there was a corresponding rise and fall in systolic and diastolic pressure and pulse rate, as shown in Fig. 13. For the majority of young and healthy subjects the systolic pressure ranges under 100 mm Hg during sleep.

These observations on a people who are known to have low arterial pressure and among whom high arterial pressure is a rare occurrence contrasted with the findings in an American university where high arterial pressure is prevalent is of clinical interest and importance.

(n) *Race*—It is a well established fact that certain people of the East have lower arterial pressure than those of the Occident. In 500 Hindus McCay³² reports an average blood pressure varying from 90 to 105 mm Hg.

Foster³³ has found that Chinese have definitely lower blood pressures than Americans. Out of a group of 35 Americans residing one year in China 23 showed a definite fall in pressure. Citing a number of specific cases one fell from 145 and 140 down to 128 and 120 mm Hg, one fell from 140 and 135 down to 125 and 108 mm Hg after two years, one a woman from 120 in United States down to 88 mm Hg in China.

An important observation on this point comes from the Sun Life Insurance Company whose records show that in 1000 policies the blood pressure values were constantly lower in Chinese than in the white population. It was also noted that there was an absence of symptoms due to low arterial pressure in these cases.

Of the various explanations offered for the low arterial pressure of the Chinese as a people the following reasons have been proposed from time to time: (1) Lighter weight of the Chinese, (2) smaller stature, (3) lowered muscle tone, (4) racial endocrine differences, (5) low protein and low salt diet, (6) climate and lower vasomotor tone, (7) absence of nervous strain. It should also be noted here that many of the observations on low arterial pressure were made in cities which are not in tropical areas. Peking for example is in the same latitude as New York.

Tung³⁴ has also observed that when Americans take up residence in China their blood pressure falls to a lower level. In a series of 58 Americans who had lived in China for a year or more the average fall of systolic pressure was 9 mm and diastolic pressure 11 mm Hg. Sixty-four per cent of his series showed this fall.

There is a unanimity of opinion that the fall in arterial pressure is not due to dilatation of peripheral vessels nor change in diet or personal hygiene. Most writers tend to believe that the important factor resides in the central nervous system and psychic life of the individual. Mental and psychic influences over the innervation of the cardiovascular system, perhaps by way of the endocrine system and metabolism, are believed to be the chief factors.

Under the discussion on blood sugar, it was already noted that the Chinese are relatively immune to both high arterial pressure and diabetes, both of which are accompanied by high levels of blood sugar.

Interestingly enough, Japanese have a higher level of blood pressure than the Chinese, for they have taken on a more western mode of living, and they have submitted to greater regimentation. It has also been shown that hypertension among urban Japanese is nearly as frequent as in America ³⁵ *It seems that those people who have not yet been influenced by modern modes of living, those who remain attuned to a quiet life and those who are content with the simplicities of life, may continue to escape the onrushing pressures which are overwhelming modern man.*

The Dean of a School of Medicine in China related to me, some time ago, the vigor and enthusiasm with which he first returns to his work after a leave of absence to America. On his return to China, he finds himself moving fast and with a keen desire to get things done, as he had been planning them while away. He then notes that those about him do not seem quite so enthusiastic as he would like and that some even look with mild disdain upon his feverishness and desire to do things promptly, in true American fashion. In a little while, however, he notes that he too is slowing up and after four to six months more, he discovers that he has become definitely synchronized and attuned to the tempo of life about him. All of which has brought him to the conclusion that there is something in the entire atmosphere of living in China which induces easement, patience and a lowering of the pressures of life.

(o) *Climature*—Arterial pressure is 10 to 15 mm. lower in the tropics. The physician in the subtropical and tropical climates sees more cases of low arterial pressure than one in the northern temperate zone.

(p) *Occupation*—Mode of living and occupation have their influence on level of arterial pressure. The writer has observed that nurses on

night duty after a period of six months or longer will not infrequently develop low arterial pressure with its accompanying clinical syndrome

3 Immunological Pathoimmunological Panel (a) *Acute Infectious Diseases*—Most acute infections are accompanied by a fall in pressure. It is this lowering of arterial pressure from the very onset of the disease that makes standing or walking difficult or impossible and forces the patient to bed and that is perhaps the main reason why the acute febrile patient falls when he attempts to get out of bed.

(b) *Acute Colds*—There is a marked fall of arterial pressure in the patient with an acute cold at the same time when he is complaining of muscle pains, shivering, cold hands and feet and general malaise at the

TABLE IV
BLOOD PRESSURE IN INFLUENZA

Cases	1st Day	2nd Day	3rd Day	4th Day
50	115	92	85	112

very beginning of these acute illnesses. This is most marked in cases of grippe and influenza. Arterial pressure reaches its lowest level during the course of epidemic influenza.

(c) *Influenza*—The writer's studies during the influenza epidemic of 1918 showed that there is a progressive fall of blood pressure from the first to the third day. In favorable cases on the fourth day the pressure remains the same or begins to rise. In a group of 50 such patients¹⁰ all had low arterial pressure, the lowest systolic pressure being 72 mm Hg and the lowest diastolic pressure being 48 mm Hg.

(d) *Pneumonia*—In pneumonia the tendency to low arterial pressure has been to some a constant source of apprehension so much so that the level of arterial pressure was used as a guide in prognosis. It is not a true guide, however. Not infrequently patients known to be of the constitutional type that have low pressure with its accompanying clinical syndrome of years' duration will go through a typical lobar pneumonia with evidence of reserve and with a good recovery even without a protracted convalescence. When pneumonia develops in one who is fatigued or exhausted from the very beginning of the disease as often happens then a low arterial pressure is of serious prognostic sig-

nificance, and its meaning is comparable to the absence of leukocytosis in the disease. A steady fall in arterial pressure may indicate progressive myocardial failure. In that case resolution is delayed, the lung surrounding the pneumonic area is congested; it shows all the physical signs of moisture and edema that increase from day to day. With this there is marked cyanosis and its usual accompaniments.

The other type of cardiovascular failure in such pneumonias bears the earmarks of vasomotor failure due to the pneumococcic toxemia. This type of patient, overwhelmed by toxemia, will show a falling blood pressure and a rapidly increasing and irregular pulse rate; all of which may terminate speedily even before the lungs become moist or wet and soggy with all the typical physical signs

TABLE V
BLOOD PRESSURE IN TYPHOID FEVER

Cases	1st Week	2nd Week	3rd Week	4th Week	5th Week	6th Week
81	93	92	83	83	85	90

(e) *Typhoid Fever*—Typhoid fever is characterized by low pressure throughout, as was shown by the writer many years ago³⁶ Here, arterial pressure descends to a lower level from week to week, as the disease progresses, reaching its lowest level during the fourth week; after which, as the disease abates, the pressure rises with the recovery of the patient.

(f) *Trichinosis*—Comparable to the low arterial pressure of typhoid fever and influenza is the low level of pressure attained in the acute infectious stage of trichinosis. This was noted by Gruber³⁷ in 1925 and Cheney³⁸ in 1926. Reports of recent epidemics by Spink and others verify this. In the epidemic reported by Spink and Augustine,³⁹ 12 out of 35 cases had a systolic pressure under 100 mm. Hg and a diastolic pressure as low as 38 mm. Hg. For the group the average diastolic pressure was 50 mm. Hg. A recent experience of the writer's covering an epidemic of ten cases, two of which were fatal, illustrated this very clearly. With the fever there is profound depression and when one considers the degree to which the entire nervous system may be involved in this disease, it is readily seen how the various circulatory controls can be altered and depressed

(g) *Chronic Infections—Focal Infections*—These are frequently found in patients with low arterial pressure. They may be a contributory depressing factor, but focal infections *per se* can account only for a small percentage of cases. Not infrequently the low pressure disappears with the improvement which follows removal of foci of infection.

SYSTOLIC BLOOD PRESSURE

682 DIABETICS

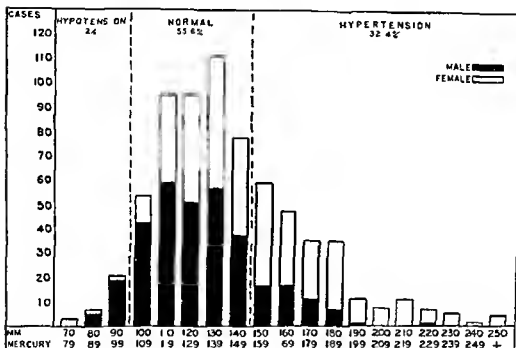


FIGURE 11 Systolic blood pressure—682 diabetics

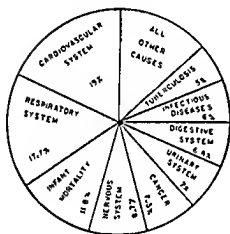
(h) *Tuberculosis*—Low pressure in tuberculosis is very common often the degree of low pressure is in keeping with the severity of the disease. But low arterial pressure is not a diagnostic criterion in cases of tuberculosis. If one were to rely too much on the level of arterial pressure in the type of patient in whom tuberculosis is commonly seen he would make many errors in diagnosis. Various studies have shown that with the patient's general improvement the level of arterial pressure tends to rise to a higher level.

(i) *Syphilis*—Low arterial pressure apparently functional in origin or possibly due to the acute infection is not infrequently seen during

the secondary stage of syphilis when the patient is toxic, mentally depressed and discouraged. If and when a decidedly low arterial pressure is found later in the disease, in all likelihood such cases will be found to have an organic basis.

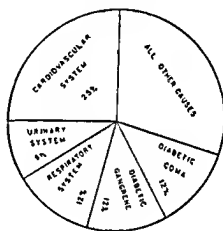
(j) *Diabetes Mellitus*—Diabetes patients show normal, high or low arterial pressure depending not upon the diabetes, but on the patient who has the disease. The chart (Fig. 14), based on a group of 682 diabetics, indicates the blood pressure levels in the group. It will be

DEATHS — ALL CAUSES

1924 — 1933
PITTSBURGH PA.

TOTAL — 76 803

DEATHS — DIABETES

1924 — 1933
PITTSBURGH PA.

TOTAL — 1475

FIGURE 14

noted that 12 per cent of the entire group showed low arterial pressure. In part this incidence of low blood pressure is due to the juvenile diabetics included in the series, in whom low arterial pressure is particularly noticeable; first because of their youth and in part due to the disease. Everyday observations in this disease have led the writer to the conclusion that during the uncontrolled period of diabetes, arterial pressure is lowered and when a normal metabolic state is reestablished, the pressure will return toward the patient's former level. Diabetes with its hyperglycemia and ketosis, when present, lowers the arterial pressure.

In the aged and in arteriosclerotic diabetics, hyperglycemia and the so-called high renal threshold are of common occurrence. In such cases

it is doubtful if the diabetic state can influence the blood pressure level and it is still more doubtful whether such influence would be favorable or desirable

While the leading cause of death in diabetic patients is given as that of the cardiovascular system (Fig 15) it must be recalled that we are still too much accustomed to think in terms of death as the result of cessation of the heartbeat and that death certificates are too inadequate to be of real scientific worth. The charts (Fig 15) compiled in 1931 show how similar are the given causes of death in diabetes and those of the general population. One needs only to glance at the recorded causes of death on a death certificate and then compare them with the post mortem report of a competent pathologist to see how much death certificates do not tell of the causes of death.

(1) *Renal Glycosuria* In one group of 41 unquestionable cases of renal glycosuria 13 had well defined low arterial pressure, i. e. under 110 mm Hg. Of the other eight only one showed a blood pressure over 130 mm systolic. Thus we have here the association of low blood sugar and low arterial pressure.

THEORIES CONCERNING CAUSATION OF LOW ARTERIAL PRESSURE

The foregoing observations cover much of the material evidences concerning low arterial pressure. When at last an underlying factor common to all these conditions is found then and only then will the whole problem be understood. Various explanations and hypotheses have from time to time been set forth as the cause of low arterial pressure.

Friedlander⁴⁰ while of the opinion that the etiology of low arterial pressure is not yet worked out, believes that loss of vasomotor tone such as is found in focal and in chronic infections is the outstanding important factor. He therefore proposed the hypothesis of capillary stasis due to the poisoning effect of histamine or histaminelike bodies.

Dally⁴¹ holds that physical and psychical efficiency depends on vitality of the somatic processes, vitality itself depending on a state of metabolic equilibrium. Disturbances of this equilibrium which in turn lead to vasomotor disturbances produce variations in arterial pressure. These variations lead to higher or lower pressure. With this in mind Dally postulated his biological law of low arterial pressure. Low arterial pres-

sure congenital or acquired temporary or permanent is always to be regarded as an expression of low vitality

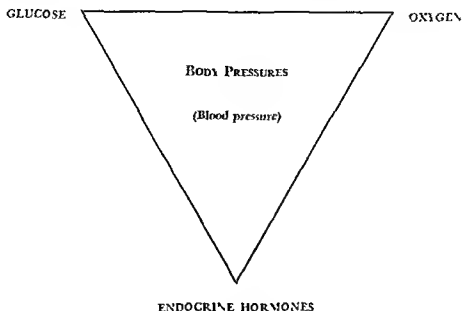
The writer¹⁰ called attention to the fact that *wherever low arterial pressure is found there are suggestive evidences of lowered respiratory function and diminished oxygenation*. The constitutional or hyposthenic type of individual the typical patient with low arterial pressure is slender undersized undernourished nonathletic. He has narrow nostrils nasal obstructions a narrow chest poor and relaxed musculature drooping shoulders low vital capacity shallow and irregular breathing all of which tend to produce deficient respiratory function and a reduction in the diffusion coefficient of oxygen with lessened oxygenation. Low arterial pressure is most striking in those acute infectious diseases in which the respiratory tract with its swollen mucous membranes and a reduced permeability to oxygen is part of the disease. Here the previously normal individual develops low arterial pressure as the direct effect of his disease. Acute infectious diseases of the upper respiratory tract influenza typhoid fever with its respiratory complications broncho- and lobar pneumonia and other acute infections are accompanied by a marked fall in pressure. Low arterial pressure is also common in uncomplicated chronic pulmonary disease. In these and in other conditions in which low arterial pressure is found there are many outward evidences of interference with normal respiratory function and oxygen utilization. Thus oxygen want and disturbed functioning of the circulatory system from the smallest capillaries to the heart proper go hand in hand where one appears the other follows.

GLUCOSE—THE FUEL OF LIFE

In 1934 the writer¹¹ first called attention to the occurrence of low blood sugars in cases of low arterial pressure suggesting its etiological significance. Further observations have confirmed this viewpoint and emphasized its meaning. It is becoming evident that the essential role here is played by oxygen and glucose and behind these two there probably is the endocrine factor. If present-day conceptions of the pituitary influence over the carbohydrate metabolism or the parts played by the adrenals thyroid and insulin mechanism prove to be correct then the endocrine hormones will come to be looked upon as catalytic agents which set off the spark for the metabolism in the presence of an available supply of

glucose and oxygen. Of course, there is always the additional influence of the central nervous system behind all of this as well as other vital functions.

This plan may be expressed in the following diagram:



This conception brings us nearer to an understanding of the etiology of low arterial pressure, whether its origin is due to an inherent defect in the organism, in the construction or quality of its parts, or when it is the pathological by-product of a disturbed state of the organism due to some disease.

PROGNOSIS

A glance at the *hyposthenic and hypotensive type of individual* (Fig. 4) quickly suggests that his physical capacity is greatly limited. Out of 55 marathon runners studied in 1909,⁴² we found that three had low arterial pressure. Before the race of 25 miles, our evaluation of their physical condition placed them in forty-third, fiftieth, and fifty-first place. In the race one dropped out in the first few miles; one ran ten miles, and the other ran 13 miles and quit. When it came to a grueling contest, these hypotensives were completely outclassed.

Harris of Pittsburgh, over a number of years, examined 1000 applicants for aviation pilot license. In studying these records, we found that

18 had low arterial pressure. A follow up of the 18 cases revealed that only three turned out to be good pilots. The others were rejected or gave up the work or were killed. Thus we see that the individual with low arterial pressure fails when placed in a position requiring physical stamina, endurance, and above all unerring and quick response in emergencies.

In disease, particularly in pneumonia, an undrifting low arterial pressure is of no decided prognostic value. However, a steadily falling pressure at any stage in the course of pneumonia is of grave import. In tuberculosis, a rising pressure comes with improvement. In organic lesions of the heart, aorta or blood vessels with an unusually low or falling arterial pressure, experience has shown that death may occur very suddenly. This does not apply to rheumatic heart disease.

In surgery, an individual with sustained arterial pressure, even if quite low at the beginning, will stand an operation as well as others, but a falling pressure is a danger signal regardless of the type of anesthesia.

Pepper⁴³ believes that in a certain proportion of cases there is a relationship between low arterial pressure and cerebral or coronary thrombosis on the basis of stagnation of blood flow. Applying this clinically, he believes that indiscriminate reduction of hypertension will favor slowing of the flow of blood, thus inviting the occurrence of a thrombus.

It may well be asked: What is the outlook for the average individual with low arterial pressure in health or disease? It is the experience of all who have studied this problem that *after middle life in the absence of an active disease, subjects with low arterial pressure have a better life expectancy than those with normal or high arterial pressure.* The lower energy index of the circulatory system in individuals with low arterial pressure suggests less wear and tear on the circulatory system. This lessened wear and tear should be conducive to the longevity which statisticians find in cases of low arterial pressure. It is not that these individuals stand the wear and tear of living better than others. More likely it is that their protective reactions to life about them are better developed than those of the average individual who with a greater abundance of energy throws himself into the fray of living and exposes himself to excesses and complications. The patient with low arterial pressure may have many symptoms and complaints, but he weathers them as well, and sometimes better, than the individual with normal blood pressure.

CASE 1 J D came to the writer in 1913 His present age is 70 He has been under the author's care for 25 years during which time gall stones and a large duodenal ulcer were removed with the establishment of a gastroenterostomy He withstood the operation well and made a complete recovery At the age of 65 he suffered intermittent claudication manifested by severe cramps in the legs A radiograph revealed large calcified tibial arteries extending from knee to ankle With care and attention this has improved and seems under control At the age of 68 he developed acute lymphatic leukemia with generalized adenopathy and a white cell count of 200 000 with 70 per cent lymphocytes This was treated with a streptococcic fraction with striking improvement and within three months the blood count had returned to normal After this he continued in good condition with a practically normal blood count Fifteen months later the entire picture of leukemia reappeared

This case is related here as an example of a man six feet two and a half inches tall weighing 170 pounds who for 25 years presented the picture of a case of low arterial pressure His systolic pressure ranged between 85 and 100 diastolic pressure 68 to 72 pulse rate 70 to 72 He had serious pathologic lesions was subjected to a major operation under prolonged anesthesia and withstood it well He had an acute leukemia with a striking recovery from what seemed a fatal disease in response to a preparation of unknown therapeutic possibilities (This preparation is still in its experimental stage and its true worth is not yet evaluated) All this happened to a patient with low arterial pressure during a full lifetime and at no time up to the present has cardiovascular failure come up for serious consideration We need not think in terms of *failing heart* when we speak of low arterial pressure

CASE 2 The writer has before him the case history of a patient who has been under his care since 1911 During the past 28 years he is now 68 years of age the patient's systolic blood pressure has varied from 90 to 110 mm Hg During these past 28 years he has worked steadily and successfully as a man of large affairs Even his giving away of \$2 500 000 for medical research has left his blood pressure unchanged and his interest in life has increased

CASE 3 This patient now aged 73 has been under the writer's care for 20 years during this time his systolic blood pressure has ranged not far from 110 mm Hg with a diastolic pressure in proportion At times particularly with mental stimulation in the course of the day his blood pressure may exceed this level More so in the last few years He first learned of his low blood pressure 27 years ago at which time his systolic reading was 76 mm Hg With this there was severe tingling sensations of the hands and feet inability to stand erect symptoms of cerebral anemia and other manifestations of a lowered vasomotor tone Through

out this 27-year period he has been a typical case of low arterial pressure. At the age of 73 he is free of evidences of organic disease. When it is stated that after a full and useful lifetime, he too has given away more than \$6,000,000 for philanthropic purposes and more than \$1,000,000 in the interest of medical education, the reader will understand the writer's interest and enthusiasm for patients with low arterial pressure.

In the last analysis these case reports reveal that the individual with low arterial pressure can live a full life and a long one, if he lives within his physical means. Under stress and strain, these individuals may have various subjective and objective symptoms, reminding them of their limitations and at the same time protecting them against injuring themselves by excesses. All of which may yet bring us to an understanding of the fallacy of the so-called "strenuous life" and the glory of dying with one's "boots on."

TREATMENT

PHYSIOTHERAPY Mr. A., at age 65, showed no evidence of organic disease but presented a complete clinical picture of low arterial pressure with a variety of nervous manifestations. In the absence of cardiovascular disease, a daily program of massage and exercises was instituted:

8 00 A. M.—Nonresistant movement and massage, 15 minutes

Abdominal massage, five minutes.

Arm and leg massage and resistant exercises, ten minutes

10-30-12 00 —Golf, 9 to 18 holes, one day and walk of $\frac{1}{2}$ to $2\frac{1}{2}$ miles on the alternating day.

5 00- 5 30 P. M.—Massage of neck, arms, back, spine and legs combined with active and passive movements

5 30- 6 00 P. M.—Relaxation and nap

Since the institution of this routine, the patient's musculature has been improved, and with this there is an almost complete disappearance of various subjective complaints. Occasionally, after an overindulgence in food or tobacco or after unavoidable nervous strain, there may be a recurrence of symptoms, otherwise he continues well. It is true that we have here a man free of organic disease, and that the cost of such a routine is prohibitive, but the important point is that elderly patients can be improved, that an atrophied muscular system can be rebuilt and that a long train of symptoms can be made to disappear and that a sense of well being in the patient can be restored, if patient and doctor will utilize the available knowledge of our day. This patient is now 73 years of age, enjoying good health and in all appearances he is in a better physical state today than he was at the age of 65.

For younger patients a course of physiotherapy of short duration is often very effective. In the last analysis massage and exercise constitute a normal and physiological effort; they are comfortable and soothing to the patient, induce relaxation and can under no circumstances do any thing but good. The pulse rate of 90 at the beginning of such a treatment will recede to between 60 and 72; mental and nervous strain subsides and a sense of well being is restored.

General Treatment. The experienced and wise doctor will succeed in the care and treatment of a patient with low arterial pressure just as he succeeds in the care and treatment of other patients. When a depressing factor in the patient's health is discovered and removed or corrected the results will be satisfactory. When the cause is not discoverable or if the frustration of a patient is beyond medical treatment or advice the physician's effort will fail. A ruined or a worried and sleepless business man may need a banker rather than a doctor for the exhaustion and psychasthenia which follow his misfortunes.

For those who by their very nature are endowed with low arterial pressure and who under ordinary circumstances are symptom free it is well to realize that nothing need be done and still more important is it to know that nothing can be done to alter the level of their arterial pressure. In these cases fools rush in where angels fear to tread.

On the other hand when there are subjective and objective clinical symptoms definitely indicating the need for interference by the physician the most effective treatment is a period of rest though not necessarily a prolonged one. And most important for morale and recovery the doctor should not tell the patient or the family that he or she has had a nervous breakdown. Many doctors who use this term freely do not know what a nervous breakdown really is. That term should be reserved for the psychiatrist who has properly evaluated the patient's reactions to frustration and defeat and knows how to deal with them and still do the patient more good than harm. It would be interesting to ask some doctors to discuss this subject before a group of intelligent medical men. It might cure them of the use of a terminology which leaves the patient mentally scarred and fearful and a ready victim for another nervous breakdown.

Removal of harmful factors organic and psychic, physical and mental, rest, a normal diet, hydrotherapy and massage, everything that can be

done to restore the patient toward a normal state should be instituted. In time, a resurgence of well being and vitality will become manifest and the patient will be restored to his normal state. It is in this type of case that the average physician has failed utterly to take advantage of the therapeutic value of hydrotherapy and massage. *With massage, with passive and active exercise properly carried out, muscle tone and muscle growth can be increased to a surprising degree, even in men of 70.*

The physician who is to handle many of these patients will find it necessary to practice both preventive and curative medicine to the full extent of his knowledge and wisdom. The things he will have to do are legion and no attempt will be made at enumerating them here. He should be a votary of eugenic marriages, he should recognize the importance of proper infant feeding, care in childhood, nutrition in child and adult life. He should realize the importance of climate, proper clothing, maintenance of normal body weight; the need for daily physical exertion, sufficient hours of rest, healthy posture; avoidance of those factors which may interfere with normal respiration; avoidance of things and situations which cause cardiac and circulatory strain; avoidance of overtaxation of the nervous system; prevention or removal and cure of infections when possible; avoidance of endogenous or exogenous intoxications; and correction of endocrine disturbances when possible. The physician who recognizes the standards of health will discern deviations from these standards and aim to correct them.

Where there is no specific disease, there is no specific treatment. Experience will prove that the single drug or special method highly recommended at one time will be superseded by another, often in rapid succession. Whatever mode of treatment the attending physician will advise should be planned for the patient with precision. The physician who has faith in the success of his treatment will unconsciously stimulate and encourage the patient to make whatever effort is necessary to give up an unhygienic mode of living and to adopt a better one. In this type of patient, as in many others, the one who lives a disordered existence and seeks cures in a bottle of medicine is on the way to disappointment.

Patients are too seldom impressed with the fact that the so-called everyday advice of the physician is really the crystallization of man's total experience, and that he who will carry out such advice in orthodox fashion is the one who will attain desired results.

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CHAPTER I

ARTERIOSCLEROSIS

By ELI MOSCOWITZ M D

Introduction The term arteriosclerosis has today a stricter connotation than formerly employed. It no longer comprises every lesion that causes thickening and hardening of the vessel morphologically and pathogenetically it is readily distinguishable from such lesions as fatty infiltration of the arteries syphilitic arteritis bacterial and infectious arteritis endarteritis obliterans thromboangiitis obliterans (Buerger) Monckeberg sclerosis rheumatic arteritis and periarteritis nodosa. More over the lesions comprised under the term arteriosclerosis are not strictly limited to the arteries but affect the capillaries and the lining of the heart chambers as well so that in most instances the term arterio-capillary sclerosis is more applicable. Under certain conditions which will be discussed later the veins may show similar changes i.e. phlebosclerosis.

PATHOLOGY

The lesions of arteriosclerosis are modified according to the anatomical structure of the portion of the vascular tree that is affected. It is now agreed that the earliest changes of arteriosclerosis are seen in the intima. There is a thickening of the subendothelial intimal connective tissue due to the proliferation of the large and small wandering cells. In the larger vessels especially in the aorta there is already an extensive infiltration with fat which is present not only within the cells but between them. Later these thickenings become deeper and more extensive forming irregular and rounded plaques bulging into the lumen. The connective tissue begins to undergo hyaline change and the fatty accumulations undergo necrosis forming an atheromatous material hence the name atherosclerosis (Marchand). At this stage changes in the elastic layer occur consisting in cleavage and interruption of the elastic layer situated at the depths of the plaques and eventually in the development of new and delicate elastic fibrils which penetrate into the new tissue

Whether these fibrils arise from the old elastic layers or from an impregnation of collagenous fibrils with elastin is still undecided.

Changes in the media are, as a rule, not seen until the later stages of arteriosclerosis. Whether thinning or hypertrophy of the muscular coat of the media occurs depends, in the writer's experience, upon whether the arteriosclerosis is of the decreascent (senile) variety, unassociated with hypertension, or whether the lesion is the result of hypertension. In the former, the media is, as a rule, thinner than normal, especially in those portions subjacent to the intimal lesion; in the latter, the media is hypertrophied. The hypertrophy is especially notable in the arterioles. The media in later stages is infiltrated with connective tissue, with corresponding destruction of the muscular and elastic elements. Round celled infiltrations are often seen, especially around the branches of the vasa vasorum. Extension of the atheromatous infiltrations into the media are not uncommon, especially when the atheroma is extensive and ulcerated. The adventitia of the vessels is little affected in any stage of the disease.

In the terminal stages, the processes become diffuse and affect almost the entire circumference of the vessel. The atheroma breaks through the intima, forming greater and lesser craterlike ulcers. The fatty atheromatous material is rich in fat and cholesterin. Infiltration with calcium and magnesium phosphate occurs, forming dense flat plaques which often fracture and project into the lumen and form a nidus for a thrombus. In these lime deposits, real bone with Haversian canals and marrow may form.

Grossly, the main characteristics of arteriosclerotic vessels of large caliber, aside from the deformity of the inner surface, are tortuosity, loss of elasticity, increased rigidity, and dilatation of the lumen. These are usually proportionate to the senescence of the process. In the smaller arteries and in the arterioles, the proliferation of the intima and the hypertrophy of the media lead to narrowing of the lumen and sometimes to complete obliteration. The consequent diminution and even loss of blood supply explains the sclerosis and atrophy of certain organs, such as the kidney.

Arteriosclerosis is a summation of many processes, one or more of which may not be present. Arteriosclerosis may be defined as a *progressive and irreversible affection of the arteries, in which hyperplasia of one or more of the structural elements is a primary reaction, with deposition*

of lipoids, collagenous tissue, hyalin and calcium as a secondary reaction the totality of both components resulting in thickening, dilatation, deformity and loss of elasticity of the walls

PATHOGENESIS

Much controversy has waged as to whether arteriosclerosis is a degeneration or an inflammatory process. The issue is more a matter of academic rather than of practical consequence and depends entirely upon personal definition of these terms. If an inflammation is regarded as a reaction of the tissue against injury arteriosclerosis is certainly an inflammation. The injury as the writer will endeavor to prove in the section upon etiology is entirely mechanical and consists in intravascular pressure whether it be normal or increased and all the lesions are explainable as far as present knowledge permits upon the basis of this normal or exaggerated function. The lesions of arteriosclerosis therefore represent a compensatory mechanism. The persistent dilatation especially in diastole causes stretching of the intima and the formation of the so-called *saftspalten*.

The proliferation of the intima is partly the result of a reactive proliferation to fill the gap and partly to a reaction around the fat that has been imbedded in the stretched tissue spaces. The splitting of the elastic may be ascribed to the stretching of the wall and growth of new connective tissue between the elastic fibrils. The hyperplasia of the elastica is a functional adaptation to counteract the increased stretching. The hypertrophy of the media when it is present is the result of the hypertension and is entirely comparable to the hypertrophy of the left ventricle under the same condition. The atrophy of the media is partly the result of the dilatation of the vessel unattended by an increased intravascular pressure and partly to pressure by the subjacent atheromatous and calcified plaques. How much of this thinning may be the result of atrophy from a lowered blood supply due to the diseased *vasa vasorum* which penetrate the media is still a question (Schlitzl).

The genesis of the hyaline deposit is not clear but as in other tissues it is entirely a degenerative product. The atheroma and consequent calcification are entirely analogous to similar processes in other portions of the body where fat and cholesterol esters form in abundance. Taken together all the changes of arteriosclerosis may be regarded as compen-

satory attempts of the tissue against intravascular tension a view originally maintained years ago by Thoma This investigator however, regarded the stretching of the media as primary and the proliferations within the intima as secondary and as attempts on the part of the tissues to maintain the caliber of the lumen This view however is now abandoned

INCIDENCE

Arteriosclerosis is universal not only in man but in all vertebrates It is a normal process incident to the senescent years Clinically arteriosclerosis gives rise to morbid states in only comparatively few Pathologically speaking its beginnings in the form of fatty plaques are already visible between the second and third decade of life This was revealed in autopsies upon German soldiers in the World War (Mönckeberg²) Thickening of the vessel is determined by palpation does not occur until the individual is well on to the fifth decade Some writers regard the fatty plaques observed commonly in infancy as already evidences of beginning arteriosclerosis but the fact that such plaques are only rarely observed in the adolescent period say between the tenth and sixteenth year led Aschoff³ to believe that these infantile plaques disappear

The probability is strong therefore that these infantile plaques represent only fatty infiltration of the intima due to the high fat diet and are comparable to the fatty infiltrations observed in animals after high cholesterol diet (Chaplow and Amischkow⁴) and in young diabetics whose blood cholesterol is high (Oppenheimer and Fishberg⁵) Strictly and biologically speaking there is no reason to regard arteriosclerosis as beginning abruptly somewhere in the third decade merely because atheroma becomes conspicuous at this age Most observers describe a physiological ageing entirely histological that begins at birth In early childhood the intima of the muscular arteries is exceedingly thin consisting only of an endothelial layer and a delicate elastic lamina As age advances the intima thickens by the growth of collagenous tissue and splitting of the internal elastic lamina occurs as early as the second year (Hallenberger⁶) The hyperplasia of the elastica proceeds into middle life The splitting begins in the larger arteries and only involves the smaller vessels after middle life (Bell⁷) The media also thickens with the growth of the body These changes have been noted in most of the sectors of the arterial tree These hyperplastic processes which

possess so many features of true arteriosclerosis may reasonably be regarded as the forerunners of the matured lesion and as Aschoff believed are compensatory to the increased intravascular pressure that proceeds from infancy to advanced life. In other words physiological ageing or functional adaptation merges slowly into disease. The intensity and distribution of arteriosclerosis vary widely in man for the same age as a general rule the writer has observed that these vary largely according to the blood pressure. Subjects dying of diseases associated with a low blood pressure for instance tuberculosis present less arteriosclerosis at autopsy than is normally seen for the same age. As shall be elucidated more fully later arteriosclerosis has no proportionate relation to age when hypertension intervenes. Arteriosclerosis under such a circumstance may even be present in infancy. In fact the writer is not aware of the presence of arteriosclerosis in infancy or the earliest years unless hypertension was present.

Arteriosclerosis begins and reaches its fruition at a slightly higher age in women than in men due in all probability to the slightly lower blood pressure in the female as compared to the male. Here again when hypertension intervenes arteriosclerosis will arise no matter what the sex. Nevertheless every clinician sees cases of premature sclerosis even under conditions of normal blood pressure so that it must be concluded that what Osler called "bad tubing" must play a role.

LOCALIZATION OF ARTERIOSCLEROSIS

The question has been frequently raised that if tension or its increased gradient hypertension is the cause of arteriosclerosis why is it that the localization of the sclerotic patches is apparently bizarre because tension being equally distributed should affect all vessels uniformly? The renal retinal cerebral splenic and coronary arteries are most frequently and most profoundly affected the pancreatic and hepatic arteries less so while the arteries of the skin the skeletal muscles and intestines least of all. Furthermore the sclerotic areas are not distributed uniformly throughout the vessel and vary in intensity in different areas for instance the posterior aspect of the aorta is more involved than the anterior while the ascending aorta is comparatively free. Erdheim⁸ has made the point that an individual with sclerosis of the ascending aorta rarely lives to be over 60 years of age. Apparently therefore other subsidiary factors beside

intravascular pressure must be determined to explain this unequal distribution

An answer for all vagaries of localization and distribution of arteriosclerosis is not at hand. One of the factors at all events is impaired expansile mobility of the vessel due either to fixation or to external resistance. It can readily be understood how any degree of fixation of a vessel will lead to an interference with diastolic recoil and the greater the diastolic pressure and the greater the fixation the greater the interference. This may explain why the severe types of clinical arteriosclerosis are more proportionate to high diastolic pressures than to high systolic and why arteriosclerosis (other factors such as intravascular pressure being equal) is usually more pronounced in solid viscera like the spleen and kidney than in the lung gastrointestinal tract or skin.

The following observations reveal the relation between impaired expansile mobility of vessels and the localization of the lesions:

(a) The patches of aortic arteriosclerosis occur earliest and are most extreme at or near the origin of the intercostal vessels which fix the posterior wall of the aorta.

(b) As a general rule the abdominal aorta which is fixed against the rigid vertebral column is more involved than the arch and the thoracic aorta which are surrounded by soft structures.

(c) Arteriosclerosis of the dural vessels is most marked in those portions that lie within the bony framework (Lauda⁹ and Erdheim¹⁰).

(d) Dow¹¹ found that the internal carotid artery was markedly arteriosclerotic in that portion that traverses the canal in the temporal bone and along the cavernous sinus. He also noted that the radial arteries when affected revealed the most marked changes in the sector that lies directly against the radius.

(e) The anterior aspect of the aorta is much less involved than the posterior which is fixed first by the insertion of the intercostal arteries and second by the rigid vertebral column.

(f) Westenhoffer¹² showed that the patches of arteriosclerosis on the posterior wall of the aorta occurred earliest at the site of prominent upper and lower borders of the bodies of the vertebrae while the hollows in between were comparatively free. The patches so to speak afford the appearance of a model in relief of the vertebral column. This observation I can affirm.

(g) In pulmonary arteriosclerosis the portions most affected are those lying against the rigid cartilaginous bronchus while that portion coursing through the soft pulmonary parenchyma are much less involved.

(h) The left coronary artery is more often affected than the right because it is imbedded in a much firmer muscular wall than the right and in a muscle subject to greater tensions

(i) In the patch of phlebosclerosis of the inferior vena cava described by Cramer and Shilling, the sclerotic area is most prominent in that position of the cava that lies against the rigid vertebral column and the adjacent aorta

There are undoubtedly other factors, which in the course of time will be described. The most promising lead has recently been devised by Wintermüt¹³ who, by the aid of injection and clearing agents, has discovered important intramural vessels in the walls of arteries the basic pattern of which is often exaggerated in arteriosclerosis. Hemorrhages from these vessels often lead to atheroma, an important finding not only because it demonstrates that lipemia is not always necessary for the production of atheroma, but also because these intramural vessels may contribute largely to the topography and localization of the lesions. His method should serve to clear up many other finer mechanisms in the production of arteriosclerosis and we await future studies with interest.

A sharp distinction, as far as incidence is concerned, between arteriosclerosis and arteriolosclerosis I have not found to be valid. There is no doubt that the sclerotic process may be more intense in one than in the other, in hypertensive disease, especially. The lesions in the arterioles are more conspicuous than when hypertension is lacking, but, by and large, arterio- and arteriolosclerosis are simultaneous lesions. It is true that the lesions of arteriosclerosis vary in different components of the vascular system, for instance, atheroma is much more extensive in the arteries of the muscular and elastic types than in the arterioles, while hyperplasia of the intima and elastica and hyalin deposits are more prominent in the arterioles.

ETIOLOGY

A multitude of factors have been assigned in the past as causes of arteriosclerosis, most of them supported by insufficient evidence, so that the cause of arteriosclerosis thus far has not escaped the domain of hypothesis. The almost constant association between hypertension and arteriosclerosis has led many observers to regard arteriosclerosis as due, in greater part at least to mechanical causes but an exclusively mechanical origin was not accepted, because arteriosclerosis (so it was argued) was witnessed so very frequently with normal intra-arterial pressure. This

latter statement involved a fallacy which strangely enough had been entirely overlooked. *Hypertension is not something new that has entered the organism in the sense of an infection, for instance, but is simply an exaggerated form of a normal function, i. e., arterial tension.*

The proofs that normal intravascular pressure and, therefore, its increased gradient, hypertension, is the only cause of arteriosclerosis will now be summarized (Moschcowitz¹⁴).

A. Incidence of arteriosclerosis of the pulmonary arteries. Arteriosclerosis of the pulmonary arteries is absolutely independent of arteriosclerosis of the greater circulation and only occurs when an increased pressure within the pulmonary circuit is present. It is most commonly seen, therefore, in all cases of mitral stenosis; next in order of frequency, it occurs with emphysema, cases with long-standing diminution in lung volume from whatever cause, bilateral pleural adhesions, certain cases of marked scoliosis, in cases of open ductus Botalli and communications between the right and left hearts; also in cardiac disorders of whatever nature that lead eventually to failure of the right heart, for instance, coronary disease, adherent pericardium, and spent Grave's disease. The mechanisms whereby such an increased resistance is produced have been set forth¹⁵ and need not be repeated here. In summary they fulfill the requirements set by Wiggers¹⁶ for the production of increased pressure in the pulmonary artery, namely: (1) The minute output of the right ventricle. (2) The resistance and capacity changes in the pulmonary circuit. (3) Back pressure produced in the left heart by changes in the systemic circuit. Under practically no other circumstances does arteriosclerosis of the pulmonary artery occur, no matter how intense is the arteriosclerosis of the greater circulation.

Arteriosclerosis of the pulmonary artery is entirely independent of age, sex, occupation, and other factors. Given the increased intrapulmonary pressure, it will occur even in infants as old as six months. The reason why arteriosclerosis of the pulmonary arteries does not occur with normal intravascular pulmonary pressure is because the normal pulmonary pressure is unusually low, according to Starling, one sixth that within the aorta. It is obvious, therefore, that arteriosclerosis affecting both greater and lesser circulations must be the exception rather than the rule. It must be remembered that hypertension does not represent an absolute but a relative value. Inasmuch as the pressure in the pul

monary artery is only one sixth that of the aorta a tension that may be normal for the greater circulation will be high for the pulmonary. Inasmuch as we have no method of determining clinically the pressure in the pulmonary circulation we do not know the optimal pressure required to bring about arteriosclerosis in this circuit but in view of the great disparity in the two pressures it is doubtful whether the systolic and diastolic pressures in the pulmonary artery ever approach the normal bronchial arterial pressure. Even assuming that the pressure within the pulmonary artery may equal that in the systemic circuit it is reasonable to infer that a normal pressure in the systemic circuit may also produce arteriosclerosis in the greater circulation provided it has been maintained over a sufficient span of time. With this independence in the incidence of arteriosclerosis of the greater and lesser circulation in mind the following syllogism seems to be justifiable. Hypertension is a heightened phase of normal tension there is a definite sequential relation of arteriosclerosis to hypertension in both greater and lesser circulations such an arteriosclerosis occurs at an early age if hypertension is present and is an inevitable lesion in all individuals past (at the latest) middle age therefore normal intravascular pressure may cause arteriosclerosis provided it acts over a sufficient span of time. In other words a road may be worn down by light as well as by heavier vehicles obviously the lighter vehicles will take a longer time. The time factor in the production of arteriosclerosis by intravascular tension is obviously of profound importance and explains why in some early cases of hypertension that have come to autopsy little or no arteriosclerosis is discovered. It also explains the progressive vascular deterioration witnessed clinically in hypertensive patients the most striking and obvious being the development and progression of retinopathy. Statistics on linear relations between pressure figures and the different manifestations of arteriosclerosis have little or no value because the biology of the disease has not been considered as well as the fact that the relation of hypertension to normal tension has not been taken into account. One may construct therefore the following equation

$$\text{arteriosclerosis} = \text{intravascular pressure} \times \text{time}$$

Obviously other factors being equal the higher the pressure the earlier the lesion will appear with normal pressures the longer the span of life necessary to produce arteriosclerosis. Under the first condition juvenile

arteriosclerosis is the result under the second decreascent arteriosclerosis or in other words the normal arteriosclerosis commensurate with age

It would be interesting to know how soon after the inception of hypertension gross arteriosclerosis begins According to the equation we submitted much depends upon the degree of the hypertension Zur Linden¹⁷ reports a case due to patent ductus arteriosus in an infant of 11 months Wajten¹⁸ reports one in an infant aged six months due to patent interventricular septum Even in the pulmonary circuit a decreascent arteriosclerosis may occur with such a low pressure as exists in this circuit In a series of 50 cases of arteriosclerosis of the pulmonary artery there were three all mild in which no mechanism that might cause increased pressure in the pulmonary circulation could be discovered They were all aged individuals the youngest being 67

B Neuroretinitis the essential lesion of which is an intense arteriosclerosis of the grosser and fine vessels of the retina only occurs when hypertension (especially diastolic) is present Simple arteriosclerosis of the retinal vessels unassociated with infiltrations or papillitis is only witnessed in people with normal or moderately elevated blood pressure who are in the senile years It has been observed (Kollert¹⁹) and the writer can confirm this that a neuroretinitis may disappear when the blood pressure drops to normal

C Arteriosclerosis is most prominent in that portion of the artery where the stress is greatest for example at bifurcations and at points of narrowing

D In congenital stenosis of the isthmus of the aorta the arteriosclerosis is most prominent or may even occur exclusively upon the proximal part of the aorta

E Marchand²⁰ found no arteriosclerosis in an extremity paralyzed by poliomyelitis while the healthy limb showed definite changes

F The endocardium of such chambers and valves as have been subjected to increased or prolonged strain shows changes comparable with those of arteriosclerosis Those of the right side are involved in hypertension of the lesser circulation those of the left in hypertension of the greater circulation and in the decreascent or senile periods of life

PHLEBOSCLEROSIS

The lesions of phlebosclerosis are identical histologically with those of arteriosclerosis The incidence of phlebosclerosis is interesting because

it reveals a definite sequential relationship to increased intravenous pressure.

1. Carrel²¹ demonstrated conclusively that a normal vein anastomosed between the divided ends of an artery became sclerosed.

2. In chronic congestion of the venous system phlebosclerosis is not uncommon (Kaya²²).

3. In hypertension of the lesser circulation due to mitral stenosis, the writer has found sclerosis of the pulmonary veins to be almost as common as the sclerosis of the pulmonary artery. An increased tension in the pulmonary veins can readily be predicated in view of the increased pressure in the left auricle. In *emphysema*, on the other hand, the pulmonary veins are normal because the resistance is within the pulmonary capillaries.

4. That phlebosclerosis is exceedingly common in varicosities is universally conceded.

5. An interesting example is that of Cramer,²³ who discovered that a patch of sclerosis in the vena cava just above the junction of the iliac veins was not uncommon in elderly individuals, and the older the patient, the commoner the lesion. He ascribes the lesion to the impinging of the two currents of blood which occurs exactly at this area; obviously, the pressure will be greater, the wider the angle of the iliac junction. The writer has been able to confirm this finding.

6. One of the most constant associations is that of sclerosis of the portal and mesenteric veins in *cirrhosis* of the liver and in portal thrombosis. All observers agree that the sclerosis is due to increased pressure in the portal system, the result of the obliteration of the portal radicles within the liver. Indeed, the validity of the concept of portal hypertension has recently been confirmed by Thompson, Coughley, Whipple and Rousselot²⁴ who measured the pressure in the splenic vein at operation by direct puncture before ligation of the pedicle. In eight cases in which the syndrome of portal hypertension was present, the pressure ranged from 250 to 500 mm. of saline solution. In three cases of hemolytic icterus the highest pressure was 125 mm. of saline solution.

7. Intense phlebosclerosis is constantly found in the venous element of an arteriovenous aneurysm (Benda²⁵).

8. In the rare cases of congenital communication between the aorta and the pulmonary artery above the cusps, Albrecht found intense sclerosis of the pulmonary artery.

9. Phlebosclerosis of the hepatic veins. This lesion which I²⁶ described some years ago is found only in patients dying after prolonged congestive right sided failure with maintenance of a high venous pressure over a prolonged period. It is always accompanied by arteriosclerosis of the pulmonary artery and by cardiac cirrhosis of the liver. The only reasonable interpretation of the mechanism is that the lesion is the result of prolonged elevated venous pressure consequent upon the hypertension of the pulmonary artery. As a consequence, the pressure in the right auricle becomes augmented; this is transmitted backward into the inferior vena cava and thence to the hepatic veins.

SCLEROSIS OF CAPILLARIES

Where capillaries are grouped together *en masse*, as in the glomerulus and in the islands of Langerhans, fibrosis, hydropic and hyaline degeneration and sometimes even calcification of the walls are frequently seen in diseases associated with hypertension of the greater circulation or with a normal blood pressure of long standing. The sclerotic changes in the islands of Langerhans account for the not uncommon association of diabetes and hypertensive diseases. That even the peripheral capillaries show similar changes under the same circumstances is evident in the tortuosity and irregularity of their contour noted by capillaroscopy by the Lombard method (Møller²⁷). In the lungs, the striking sclerosis of the capillary wall noted in diseases associated with hypertension of the pulmonary circuit has been described (Moscowitz²⁸). These capillary changes are never seen unless arteriosclerosis of the pulmonary arteries is present and they represent essentially the dominant lesions of brown induration of the lungs.

"PRIMARY" ARTERIOSCLEROSIS

If the causal relation between intravascular pressure, whether normal or raised, is acknowledged, the term "primary" arteriosclerosis loses justification. It seems peculiar that the term "primary" should only be applied to the arteriosclerosis of the pulmonary artery and especially to those extremely rare cases in which no obvious cause, such as mitral stenosis is found. It is acknowledged that, with these exceptions, arteriosclerosis of

the pulmonary artery is always secondary to conditions causing increased pressures. The number of recorded cases of primary pulmonary arteriosclerosis is few. I have examined many of the reports and when sufficient data are available few pass the hazard of a strict critique. In many the lesion is not strictly an arteriosclerosis but an acute or subacute arteritis, probably of infectious origin. In some, the condition is the phenomenon known as idiopathic dilatation of the pulmonary artery (Oppenheimer²⁹). The cause of the anomaly and the site of obstruction is obscure. In many, the clinical data indicate cardiac disorder consequent upon coronary disease or hypertension with left, and eventually, right-sided heart failure. In the largest number, a lesion such as emphysema, bronchiectasis, pleural adhesions, or infiltrative processes in the lung are ignored. This last remark is particularly pertinent to that much discussed malady known as "Ayerza's disease." Ayerza originally regarded these cases of "cardiacos negros" as primary arteriosclerosis of the pulmonary artery of syphilitic origin. Later, his pupils, Arrillaga³⁰ and Escudero³¹ modified the conception; they excluded syphilis as the cause but still regarded the sclerosis as primary. These authors, however, completely ignored bronchiectasis, emphysema, or a chronic bronchitis which they reported as being associated in all their cases. In other words, Ayerza's disease is neither syphilitic nor primary. The introduction of this term into medical nomenclature is unfortunate. Syphilitic sclerosis of the pulmonary artery occurs, though rarely, but it does not produce the clinical picture of "cardiacos negros." It must be insisted upon that it is not the arteriosclerosis of the pulmonary artery that produces the clinical picture, but the hypertension of the pulmonary circuit that brings it into being. In other words, the sclerosis is the result and not the cause.

EXPERIMENTAL ARTERIOSCLEROSIS

Much of the older work on experimental arteriosclerosis is vitiated by the fact that the rabbit, the animal most frequently employed, is subject to spontaneous arteriosclerosis. There are only three methods that have stood the test of consideration: (1) By adrenalin; (2) by ergosterol feeding; (3) by a high cholesterol diet.

1. The adrenalin type is now regarded as identical with the so-called arteriosclerosis of Mönckeberg, which essentially consists in a calcification of the media and is different morphologically and pathologically from

true arteriosclerosis. The mechanism whereby adrenalin produces these changes is not clear.

2. Feeding with large quantities of ergosterol causes necrosis of the media with calcium deposition not only in the aorta and its larger branches but in the pulmonary artery as well so that the end result is like that produced by adrenalin.

3. The cholesterol arteriosclerosis first produced by Anitschkow³² and since repeatedly confirmed reproduces most of the features of true human arteriosclerosis especially in relation to the size, shape and distribution of the lesions. Nevertheless there are marked points of difference between this variety of experimental arteriosclerosis and human arteriosclerosis. These are: (1) The lesions have thus far been obtained only in herbivora and but rarely in carnivora and then only when a hypercholesterinemia is produced that is so high as to be unphysiological. The reason may be as Schonheimer³³ has suggested that herbivorous animals cannot excrete cholesterol. (2) In man no rise in blood cholesterol is ever obtained. Indeed there is no consistent relation between the blood cholesterol and arteriosclerosis in the human being (Peters and Van Slyke³⁴).

4. The writer has seen sections of the vessels of such experimental arteriosclerosis in rabbits and finds only a deposition of lipid in the intima. There are none of the compensatory effects in the elastica and the media.

5. The lipid depositions are not limited to the arteries but occur in the veins and indeed in the entire reticuloendothelial system.

The probability is strong therefore that cholesterol arteriosclerosis represents nothing more than a lipid deposition in the intima similar to that found in infants on a high fat diet, in diabetes when lipemia arises (Oppenheimer and Fishberg³⁵) and in the lipemia of nephrosis (Lowenthal³⁶). Duff³⁶ whose comprehensive article is commended concludes that there are important differences between experimental and human arteriosclerosis and that the results of experimental arteriosclerosis cannot be strictly applied in the interpretation of the human variety. Hypercholesterinemia cannot be regarded as the cause of the lesions in the arteries. He believes that some form of injury attendant in the experimental procedure of cholesterol feeding is the primary event in the development of the lesions of experimental arteriosclerosis. The nature

of this injury is unknown to Duff but to the writer the results of experimental arteriosclerosis can be reconciled to the known findings in human arteriosclerosis by assuming that given a prolonged or exaggerated intravascular pressure the normal cholesterol content of the blood can be mechanically pressed into the normal *saftspalten* of the vessel

In this interpretation a hypercholesterinemia is not essential in the production of arteriosclerosis. Obviously if an excess of cholesterol is present the lesions will appear earlier or be more intense. Fundamentally the issue hangs on whether one views lipid depositions as an indispensable lesion of arteriosclerosis or only a facultative one. In other words is arteriosclerosis primarily a metabolic disturbance or not? Is arteriosclerosis synonymous with atherosclerosis or not? Those who regard lipid changes as the primary factor have held that the fatty deposits almost universal in the aorta of infants represent already the beginnings of arteriosclerosis.

However there is evidence that these deposits are reversible because they are not found in older children. Moreover sclerosis by intimal thickening and hyperplasia of the elastica can occur without the initiation of lipid deposits. This is demonstrable in many of the muscular arteries of the extremities and especially in the arterioles and in areas of arteriosclerosis far distant from the atheroma. Furthermore sclerosis without lipid is seen frequently in arteriosclerosis of the pulmonary artery. Finally if phlebosclerosis can be regarded as an analogous process to arteriosclerosis the complete absence of lipid in most instances is convincing testimony that sclerosis may occur without lipid deposition. At best Anitschkow may have produced athero but not true arteriosclerosis.

It must be admitted therefore that thus far all attempts to reproduce experimentally arteriosclerosis in the greater circulation have thus far failed and deservedly so because these experiments have not taken into consideration the primary element in the production of arteriosclerosis namely intravascular pressure. In the past few years Goldblatt³⁷ has finally succeeded by narrowing the renal vessels in producing maintained hypertension in the greater circulation. Thus far his reports on the production of arteriosclerosis are still incomplete and we await his further publications with reference to this point with interest.

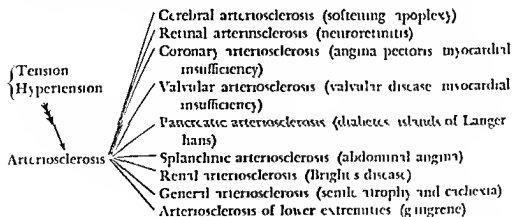
RELATION OF INFECTIONS, FOOD, PRODUCTS OF METABOLISM, POISONS, ETC., TO ARTERIOSCLEROSIS

The independence in incidence not only between arteriosclerosis of the greater and lesser circulations but also between the sclerosis in the arteries and the veins and the absolute relation of arteriosclerosis of the pulmonary vessel to pressure changes prove at once that substances that bathe both circulations and the entire vascular system simultaneously, such as infections, toxins food, and metabolic products cannot be regarded as causes of arteriosclerosis. The only way in which such substances might possibly cause arteriosclerosis is by assuming that a selective action occurs, but this is untenable in view of the consistent relation of arteriosclerosis to pressure changes.

It is necessary in this relation to emphasize the fact that infections cause lesions of the vessels, but such lesions represent an arteritis or a phlebitis and are different in every particular from those of arteriosclerosis. Syphilis, therefore, does not produce arteriosclerosis.

CLINICAL IMPORTANCE OF ARTERIOSCLEROSIS OF THE GREATER CIRCULATION

Arteriosclerosis by itself rarely kills. In cases following hypertension it is the hypertension and the consequences of the sustained elevation of the blood pressure that usually compromise health. Diagrammatically these eventualities may be represented as follows:



When the arteriosclerosis is the result of long sustained normal blood pressure (decremental arteriosclerosis of Allbutt senile arteriosclerosis), the same diagram is applicable. In such individuals the morbidity from the arteriosclerosis is usually the result of localized thrombosis or from an

embolus derived from a clot on one of the diseased plaques. The regions most often affected by such vascular accidents are in order of frequency the coronary vessels, the cerebral vessels and the vessels of the lower extremities.

The clinical phenomena of the various regional arteriosclerosis outlined above cannot be discussed within the limits of this exposition for those interested the reader is referred to the chapters under these various headings.

ARTERIOSCLEROSIS ASSOCIATED WITH DIABETES

The frequent association of arteriosclerosis and diabetes has led many observers to believe that diabetes causes arteriosclerosis but many young diabetics have been followed over a period of many years without any manifest arteriosclerosis developing. Indeed all the evidence tends to prove the direct opposite *viz.* that diabetes is usually the result of a capillary sclerosis of the islands of Langerhans. Kramer³⁶ found hypertension in 39 per cent of all diabetics. It is necessary at this point to call attention to the fact that the fatty deposits on the aortic intima often witnessed in young diabetics do not represent true arteriosclerosis but are infiltrations resulting from the associated lipemia and are identical with the lesions obtained in experimental arteriosclerosis by high fat feeding.

So called diabetic gangrene of the extremities is therefore strictly speaking arteriosclerotic gangrene, the diabetes being only a complication.

MÖNCKEBERG ARTERIOSCLEROSIS

This type of arteriosclerosis is characterized by deposition of lime in trachealike form within the media of the arteries with no or only slight changes within the intima. The bulging of these deposits within the lumen causes narrowing of the lumen and depressions in the inner wall of the vessels between the deposits. The lime often undergoes osseous transformation. The calcareous deposits are easily visible by x-rays. This type of arteriosclerosis is particularly common in the vessels of the extremities and imparts a beaded feel to the palpating hand. It occurs as a rule in the advanced years and is therefore associated with genuine arteriosclerosis. Clinically it is of little consequence. The cause of Monckeberg arteriosclerosis is not known. In this connection it is well to recall that experimentally animals given excessive doses

of ergosterol acquire, among other forms of metastatic calcification, lime deposits in the media of vessels that bear a strong resemblance to the arteriosclerosis of the Monckeberg type (Schiff³⁹) The experimental arteriosclerosis obtained by adrenalin is also of this nature (Josue)

PSEUDO- OR TRANSIENT ARTERIOSCLEROSIS

This clinical concept, first described by me in 1928⁴⁰ is occasionally observed in the course of an acute glomerulonephritis in young individuals In the early phase of this malady, the radial arteries on palpation feel hard and thickened, the blood pressure is elevated, and the diagnosis of arteriosclerosis is made and appears justified, a bad prognosis is, therefore, given The case is usually diagnosed as an 'acute exacerbation of a chronic nephritis' If the patient recovers, this feel of thickened radial vessels disappears The feel of the thickened vessel is not due entirely to the hypertonus itself, because the feel persists for two or three weeks after the blood pressure returns to normal It is in large part due to the hypertrophy of the media that is compensatory to the increased intravascular tension analogous to the hypertrophy of the left ventricle that occurs in hypertension of the greater circulation Of nine cases in which this phenomenon was observed by the writer, one came to autopsy and the aorta was entirely normal

RELATION OF RACE TO ARTERIOSCLEROSIS

Statistics on the racial incidence of arteriosclerosis are notoriously unreliable for many reasons (1) Because many observations are concerned only with clinical arteriosclerosis (2) because mortality tables relate only the cause of death and not associated lesions, and (3) because post mortem diagnosis of arteriosclerosis is usually made only on the presence or absence of atheroma When we consider that the beginnings of anatomical arteriosclerosis are already visible at a very early age the study of statistical arteriosclerosis seems very futile, because the percentage of incidence will be close to 100 per cent More valuable would be data as to how early the grosser lesions of arteriosclerosis appear in different races, but such data are not available In respect to clinical arteriosclerosis a statistical study of racial incidence may be worth while Inasmuch as the majority of cases of clinical arteriosclerosis (meaning thereby, occlusive arterial lesions cerebral hemorrhage, and chronic nephritis) are associated with hypertension a study of the racial incidence of hyper

tension may serve as an indirect method of studying this problem. Hypertension is supposed to be less frequent in Japan (Volhard⁴¹) China (Cadbury⁴² Foster⁴³) and in Eskimos (Thomas⁴⁴) and indeed these writers state that the incidence of clinical arteriosclerosis in these countries is less than in countries where hypertension is more common.

Of particular interest to us in this country is the notable rise in the frequency of hypertension and clinical arteriosclerosis that has occurred in our northern negroes in the past decade or two. Moreover it is our impression in Mount Sinai Hospital and confirmed by Jaffé⁴ that once hypertension enters it is more liable to pass into the malignant phases than in whites. That this rise is due to environmental factors is shown by the fact that in uncivilized Africa the black natives are notoriously free from hypertensive disease. Thus Donnison⁴⁵ in Kenya Colony observed no instance of hypertension or chronic interstitial nephritis in 1800 hospital cases. The reason for this extraordinary rise in hypertensive disease is a mystery. It cannot be diet because diet in so far as it is high caloric does not induce hypertension; moreover the diet of northern negroes has not changed. It cannot be climate because this has not varied. Inasmuch as certain varieties of essential hypertension are in my opinion the result of psychological conflicts I suspect that industrialization and the competitive forces of modern civilization are the dominant environmental factors.

RELATION OF HEREDITY TO ARTERIOSCLEROSIS

The study of the problem of heredity and arteriosclerosis offers difficulties similar to those concerning the relation between race and arteriosclerosis. All studies heretofore have been directed toward the incidence of clinical and not to anatomical arteriosclerosis and therefore indirectly toward the greatest conditioning factor, namely, hypertension. The problem therefore gravitates upon the genetic relation between hypertension and arteriosclerosis. In addition other difficulties are involved: the fact that observations of families are made only rarely on more than three generations; that the histories are often ones of hearsay and the diagnosis is unreliable; that families are often too small to base an adequate computation; that the individual members of a family may die before the hypertensive age has been reached; and finally, with a malady so common the laws of chance would make the occurrence of hypertension very probable in more than one member of a family or in two or more

generations. Nevertheless despite these handicaps sufficient data have accumulated that show that hypertension occurs in families higher than the mere laws of chance would allow. Thus O'Hara, Walker and Vickers⁴⁷ found that in 68 per cent of a group of hypertensives there was a history of some manifestation of arteriosclerotic disease such as apoplexy, heart disease, nephritis, arteriosclerosis and diabetes while of a control group only 37.5 per cent presented a history of familial vascular disease. They concluded that a family history of vascular disease is almost twice as common in a patient with hypertension as in one without. Reports of the familial incidence of hypertension are too numerous to quote in detail but Weitz's⁴⁸ report is interesting because his studies were well controlled. The following table shows the number of hypertensive relatives in a series of 82 proven hypertensive patients.

In three generations	6
In one parent or both and in several siblings	13
In one parent or both and in one sibling	22
In one parent or both only	22
In several siblings only	3
In one sibling only	10
In none of the relatives	6

Thus in 76.8 per cent, one or both parents gave a history of having died from some form of arteriosclerosis while in a control series only 30.3 per cent died of similar conditions. Moreover Weitz found that the parents of hypertensives died at an earlier age than those of the non-hypertensives or control group and that the siblings of the hypertensive patients presented higher systolic pressure than the siblings of nonhypertensives. When one takes into consideration that some of the hypertensives had lost siblings from hypertensive disease the incidence of hypertension in their siblings would have been much higher. Weitz believes that there is an "anlage" for the development of hypertension that it does not appear until the later years of life and that in the Mendelian sense it is a dominant quality.* These findings are in accord with impressions obtained by clinicians with long experience. Many years ago Osler called it "bad tubing." However as in many problems concerning the heredity of acquired characters the question as to how much

* That "anlage" may only appear later in life is proven by the investigations of Conner⁵⁰ in pernicious anemia. He found an extraordinary high percentage of achlorhydria in relatives of patients with pernicious anemia whereas achlorhydria is unknown in infants.

of a tendency is genetic and how much is the result of environmental factors cannot be so easily answered. In other words in how far is the constitution for hypertension genotypic or phenotypic? I am afraid that until a race of animals with hypertension can be developed in which breeding can be controlled without the cultural and the host of other environmental factors that affect man a precise answer will probably never be given. In a previous paper⁴⁹ I tried to show that hypertension is definitely related to environmental factors that such factors are sometimes far reaching is evident in the enormous difference in the incidence of hypertension in negroes in their native habitat and in civilized countries. The mere fact that a child of a hypertensive father develops hypertension does not give one the right to conclude that he has inherited it.

Temperament and character are often imitative. As the problem stands at present therefore all that one can say is that the constitution is probably composed of both genotypic and phenotypic characters but in what proportions and in what relations is difficult to say.

DIAGNOSIS OF ARTERIOSCLEROSIS

The conventional method of diagnosing arteriosclerosis by palpation of the radial artery and by observing the tortuosity of the temporal arteries is of little clinical consequence because this thickening and tortuosity are late phenomena and furnish inadequate information concerning the condition of the remaining arterial tree. Furthermore palpation furnishes information concerning the condition of the media alone. Fischer and Schlayer⁵¹ have shown that when the arteriosclerosis is limited to changes in the intima the artery is not thickened to the palpating hand. As they have shown (and this observation has been confirmed by the writer) the feel of thickening is the result of actual hypertrophy of the media or of hypertonus itself.

In the last analysis the determination as to whether thickening of the vessel is present or not adds but little practical information to the clinician because as has already been pointed out it is the fundamental functional change (hypertension) that leads to clinical disorder and not the arteriosclerosis *per se*.

For the determination of anatomical arteriosclerosis probably the best method is that of A. V. Hill who devised a hot wire galvanometer that is extremely sensitive to the slightest puff of air. By applying this

instrument in connection with a double string electrocardiograph, the rate of the pulse wave velocity is determined. Inasmuch as the pulse wave velocity is directly proportionate (diastolic pressures being equal) to the elasticity of the vessel wall, it was found that this velocity was increased in arteriosclerosis, and the more intense the arteriosclerosis, the greater the velocity. For clinical purposes, here again, the value of such determination would not be great, but it should prove of value if determined periodically to ascertain the progress of the lesion.

PROPHYLAXIS

Inasmuch as arteriosclerosis of the greater circulation is a normal involutionary process, the so-called descrescent arteriosclerosis of the senescent years cannot be prevented. Prophylaxis only plays a rôle in respect to the arteriosclerosis that arises from hypertension. This involves the problem of the cause, prevention, and treatment of hypertension, for which the reader is referred to the chapter on this subject. At the present, all that need be said is that hypertension is essentially a by-product of civilization, and the result of a lack of adjustment between the individual and the swiftness and complexity of modern life. The writer believes much can be done, especially by educational and by dietetic treatment, to prevent, arrest, and slow the progress of hypertensive disease.

TREATMENT

It is obvious that once arteriosclerosis of the greater circulation has developed, nothing can be done to restore the artery to its normal texture, for the simple reason that normal intravascular pressure can not be eliminated. The most that treatment can do is to partially or completely restore the function of the organs that show clinical damage. Speaking in general terms, the treatment of arteriosclerosis may be discussed under the following headings:

1. Educational: It is well at the beginning of treatment to allay the fears of the patient. "Hardening of the arteries" is always associated in the patient's mind with general decrepitude, apoplexy and sudden death. The patient should be instructed that arteriosclerosis is often compatible with longevity, and that even when certain vital organs show some damage, reasonable care may prolong life indefinitely. If the patient has hypertension, he need not be told all the possible dire consequences. Unless certain organs, such as the brain, the heart, or the kidneys are

greatly compromised the patient should not be made to feel he is a confirmed invalid and that all activities not directly concerned with the pursuit of health should straightway be abandoned. *Under ordinary circumstances, therefore, it is unwise to advise complete retirement from business, unless the business involves too great a physical and more especially a mental strain.* Such advice is given altogether too lightly and too frequently and experience is common that such individuals go to pieces rapidly after retirement for the reason that they as a rule have no real interest outside of their business. They become morbid, self-absorbed and deteriorate mentally and death comes within a few years.

2 Exercise and Rest. Unless the heart is seriously damaged or the function of the lower extremities is compromised by arteriosclerotic gangrene exercise is an important adjuvant in the treatment of arteriosclerosis. Exercise is of benefit for a number of reasons. (1) It maintains the patient in an athletic condition, a state of being that cannot be measured in physical terms and which may be defined as that state which obviates the feeling of lassitude. (2) By increasing oxygen content it increases the basal metabolic rate and thus contributes to a loss of weight. Other things being equal patients with arteriosclerosis are usually better physically and feel better when they are thin than when they are overweight. This applies especially to those patients whose arteriosclerosis is associated with hypertension. (3) Exercise opens the reserve capillary bed (Krogh) and thus lowers the peripheral resistance. There is no doubt that the maintenance of a high diastolic pressure is in part the result of an increased resistance in the peripheral capillaries. (4) When the arteriosclerosis is associated with diabetes the value of exercise in raising tolerance is acknowledged (Joslin¹⁰). Exercise for arteriosclerotic patients should never be violent. The best method is walking and golf. Gymnastic exercises have been found by the writer to be of little avail. Horseback riding is also applicable in many instances.

Rest is only indicated when the general condition of the patient is extremely poor and when the heart and extremities are affected. The patient should be encouraged to take frequent and extended vacations not for the purpose of rest but in order to stimulate fresh impressions. It is change, not rest, that is essential. For this reason nonarduous travel is more to be preferred than a monotonous hotel existence. The writer has not observed that spa treatment is of any value to patients afflicted

with arteriosclerosis except in cardiac affectations and then the value of the treatment lies not so much in the waters as in the change of scene and the regulation of the daily regime and the diet

3 Diet It has already been shown that diet has no influence upon the development of arteriosclerosis itself Nevertheless the matter of diet has a very profound influence upon certain of the sequelae of arteriosclerosis: *i. e.* the cardiac (myocardial insufficiency coronary disease) the pancreatic (diabetic) and the renal (Bright's disease) It also has a very important bearing upon the most important precursor of arteriosclerosis namely hypertension It is now well established that such patients when overweight are decidedly benefited by a reduction cure and the only kind of a diet that is at all indicated in such conditions is other things being equal one of low caloric value Such a diet must necessarily be high in protein and low in fat and carbohydrate It is for this reason that the conventional low protein diet for arteriosclerosis and hypertension does more harm than good because the carbohydrate and fat substitutes increase the body weight

It is obvious that when azotemia has developed in the course of renal disease a low protein diet is indicated When arteriosclerosis is present in a lean person or one of normal weight diet is of little avail except to maintain the weight at the point of maximum efficiency There is no point whatever in excluding condiments Salt is cut down not so much because it has any effect upon the hypertension but because excessive salt will cause thirst and thus bring about water retention which is one of the important elements in maintaining excessive weight Alcohol has no effect whatever upon arteriosclerosis except insofar as it contributes to the gaining of weight It is therefore better in most instances to exclude it Coffee and tea are not contraindicated in arteriosclerosis unless the patient's sleep is affected thereby Smoking is also not to be interdicted unless the patient has coronary disease In such instances the effect of the absorption of nicotine is profoundly detrimental (Moscowitz²³)

4 Drugs No drug has thus far been discovered nor indeed (judging from the genesis of arteriosclerosis as it has been outlined) is it likely that a drug will ever be found that will cure the arteriosclerotic lesion The only way in which drugs may be useful in arteriosclerosis is by influencing the function of organs damaged by the lesion

Potassium iodide which hitherto has been most widely employed in the treatment of arteriosclerosis has not proved of any value whatever. Its employment in arteriosclerosis probably dates from its proven value in syphilis but as everybody has shown syphilitic arteritis is not arteriosclerosis. Rosenthal⁶⁴ reports that iodine administered to cholesterol fed rabbits prevented the deposits of lipoid in the aorta. He believes this action is dependent on increased thyroid activity. However this effect cannot be consistently applied to the treatment of human arteriosclerosis. Nitroglycerin has been employed in arteriosclerosis because it reduces blood pressure. Its effects however are very transient and it is therefore of influence only in relieving spasmodic symptoms associated with arteriosclerosis such as the pains of *angina pectoris*. The caffeine preparations are useful in arteriosclerosis only in such instances where diuresis is essential as in cardiac or nephritic dropsy. Inasmuch as certain caffeine derivatives such as *diuretin* and *metaphylline* have been shown to dilate the coronary arteries these preparations have proven of value in lessening the frequency and intensity of *anginal pains*.

Sedatives such as *chloral*, the *bronudes* and the *coal tar hypnotics* are indicated in arteriosclerosis when the patient is *restless* and a poor sleeper. Under such circumstances the effects of these drugs upon the hypertension is often very real. Otherwise the indiscriminate use of these remedies in arteriosclerosis is to be deprecated. The patients are often depressed already and to make them more so by the use of depressing drugs is unwise. *Digitalis* is a sovereign remedy in many of the sequelae of arteriosclerosis especially in myocardial insufficiency and in some of the cardiac arrhythmias *extrasystoles* *auricular flutter* and *fibrillation*. Its indications here are the same as those in cardiac conditions from whatever cause. Hypertension in itself is now no longer regarded as a contraindication to its use.

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CHAPTER LI

PERIARTERITIS NODOSA

By DAVID L. FARLEY M.D.

Synonyms Polyarteritis acuta nodosa polyarteritis nodosa periarteritis nodosa

Definition Periarteritis nodosa is characterized by a peculiar involvement of the walls and adventitia of the medium sized arteries and the formation of nodules along the course of the vessels

Review of Literature Kussmaul and Maier in 1866 first described periarteritis nodosa. As in the case reported herewith a tentative diagnosis of trichinosis was made in their case subsequently proven to be a mistaken diagnosis by biopsy. Harris Lynch and O'Hare in June 1939 were able to find 95 cases in the English literature. They add six cases making a total of 101 cases. Their table showing frequency of symptoms and signs in 101 cases is inserted in this article.

ETIOLOGY

The disease is rare. In the reported cases it has occurred more frequently in men than in women. It is said to occur spontaneously in certain members of the deer family. The exact etiological agency has not been definitely determined. Considerable work has been done with guinea pigs, rabbits and monkeys in the attempt to settle definitely the question of etiology. Streptococci and filtrable viruses have been put forward as causing the disease.

PATHOLOGY

The lesions of the disease are most interesting. Along the course of the arteries involved small projecting nodules are scattered. These nodules vary in diameter from 3 mm. down to some which cannot be recognized with the naked eye. The nodules may run together or be distributed at intervals of 1 to 2 mm. The lesions are most apt to occur abundantly in the mesenteric arteries of the capsules of the abdominal viscera. However the distribution may be very widespread involving also the vessels of the skin, heart and brain. The microscopic appearance

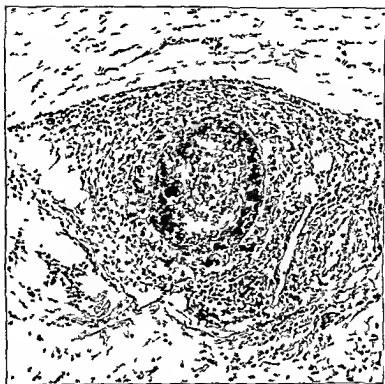


FIGURE 1 Photomicrograph of typical lesion in gastrocnemius muscle obtained at biopsy. Note necrosis of media, palisade of mononuclears about it and inflammation in adventitia $\times 97$ (Taylor and Farley, Bull.AYER Clin. Laboratory.)



FIGURE 2 Photograph of mitral valve showing (a) thickening of edges of valve and chordae tendineae, (b) prominent vessels extending to edge of valve and (c) periarteritic nodules along them (Taylor and Farley, Bull.AYER Clin. Laboratory.)

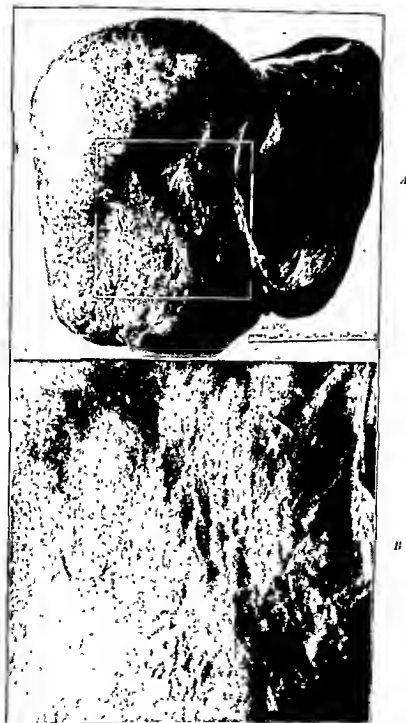


FIGURE 3. *A*, Photograph of anterior surface of liver showing thickened capsule over depressed scarred area in which periaarteric nodules are seen. *B*, Enlarged view of area indicated in *A*. (Taylor and Farley. Bull. Amer. Clin. Laboratory.)

of the lesions is perhaps the most characteristic feature of the disease. The media and adventitia of the vessels are infiltrated with polymorphonuclear leukocytes. Areas of necrosis are found most frequently in the medial coat but may also be seen in the adventitia. There may be abrupt transition from a necrotic portion to the unaffected part of the vessel wall. The arteries of nerve trunks may be involved. In a case seen by the writer the coronary arteries showed striking nodularities. The capsules of the liver and spleen may show generalized thickening with

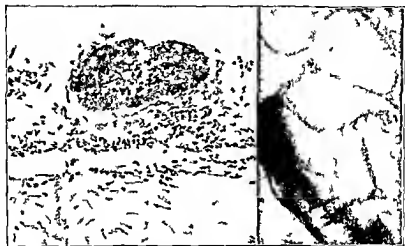


FIGURE 4. A Photomicrograph of a nodule on the vascular surface of the intimal leaflet of aorta. B Photomicrograph of nodules in the arterial wall of the brain. (Taylor and Farley. B. H. A. Clin. Laboratory.)

opaque strands of tissue made up of collapsed arteries with nodules along their course.

SYMPTOMS

The symptoms of the disease follow from the situation and extent of involvement of the arteries. Because of this fact the symptomatology is so baffling in extent that the diagnosis is seldom arrived at directly. There is usually moderate fever. The disease pursues a subacute course with gradual decline in the patient's condition. Involvement of the nerve trunks may lead to weakness of muscles, pain, atrophy, anesthesia and paralysis. The tendency of the formation of aneurysms along the course of the vessels may give rise to rupture and hemorrhage with its attendant symptoms. For example in the brain there may be a sudden apoplexy.



FIGURE 5. *A*, Photomicrograph of section of a nodule along a coronary artery showing giant cells forming a part of the inflammatory reaction in the intima. $\times 100$. Insert shows enlarged view of two giant cells. $\times 416$. *B*, Photomicrograph of section taken through a nodule along a coronary artery showing adventitial necrosis. $\times 87$. (Taylor and Farley: Bull. Amer. Clin. Laboratory (1972))

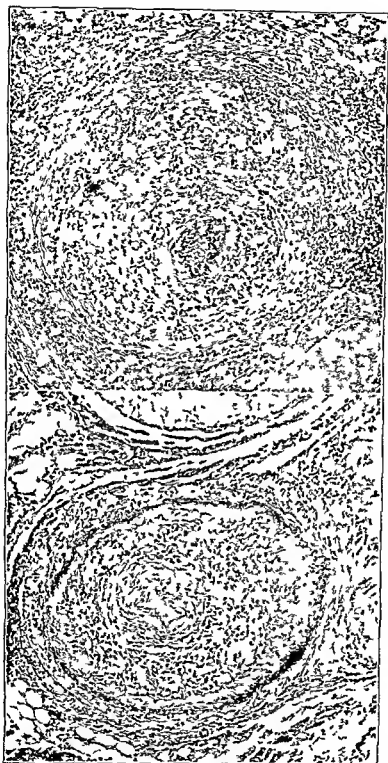


FIGURE 6. *A* Photomicrograph of section of nodular structure $\times 81$. *B* Photomicrograph showing lesion in one of the arteries in a nerve trunk from sacral plexus $\times 91$ (Taylor and Fleury, Bull.ayer Clin. Laboratory)

FREQUENCY OF SYMPTOMS AND SIGNS IN 101 CASES OF PERIARTERITIS NODOSA*

	Frequency		Frequency
Fever	80	Headache	29
Leukocytosis	70	Arthritis	27
Albuminuria	65	Atrophy	25
Rapid onset	58	Visual disturbances	23
Abdominal pain	57	Purpura	22
Edema	52	Cyanosis	21
Loss of weight	48	Eosinophilia	19
Neuritis	48	Nausea	17
Hematuria	47	Nodules	16
Hypertension	46	Pain in the chest	16
Dyspnea	41	History of allergy	15
Weakness	41	Convulsions	15
Emaciation	36	Icterus	12
Cough	36	Vertigo	8
Vomiting	31	Positive serologic reaction	8
Sensory involvement	31		

* Periarthritis Nodosa. Harris Alfred W. Lynch George W. and O'Hare James P. Arch Int M 63 1163 (June) 1939

DIAGNOSIS

In recent years relatively more cases have been diagnosed before death because of more frequent use of biopsical methods. Not infrequently the clinical condition suggests trichiniasis. In a number of cases there has been a well marked eosinophilia. Section and study of the excised tissue leads to the correct diagnosis. In reported cases, the leukocyte count has varied from normal to 30,000 or 40,000 per cmm. In a case reported by Osler, the count finally reached 116,000 per cmm. There may or may not be eosinophilia. In the case reported by J. Spottiswood Taylor there were 72 per cent eosinophiles, 22 per cent neutrophiles and 6 per cent lymphocytes with a total count of 25,700.

PROGNOSIS

The prognosis is usually fatal. Jager has suggested that cases may be overlooked, may recover, and that the true nature of the condition only becomes apparent at necropsy. A better method for diagnosis would enable the clinician to establish the milder cases of the disease. This desideratum depends upon, no doubt, the definite establishment of an etiological agent.

TREATMENT

This is symptomatic. General measures, such as rest in bed, nourishing diet, fresh air and sunshine are indicated. Rupture of an aneurysm in the vessels of the brain or elsewhere often mark the end of the active course of the disease.



FIGURE 7 Photomicrograph of longitudinal section through a branch of the mesenteric artery showing the distribution of nodules along its course. $\times 13\frac{1}{4}$ (Taylor and Farley, Bull. Amer. Clin. Laboratory)

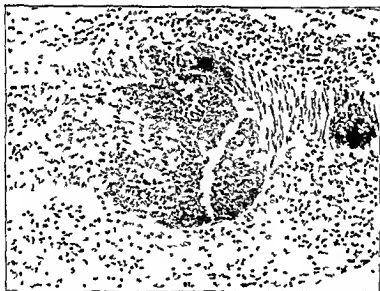


FIGURE 8 Enlarged view of rectangular area shown in FIGURE 7. Note abrupt transition from necrotic portion to the unaffected part of vessel wall. $\times 127$ (Bull. Amer. Clin. Laboratory)

CASE REPORT M. W., white female, 35 years of age, the present illness began in May 1932 when both feet became swollen and somewhat painful. She developed signs which her physician interpreted as serum sickness although there was no record of serum having been given. Shortly after this episode her asthmatic attacks ceased with rather startling suddenness, never to return, and her feet greatly improved. Three weeks before admission to the Cooper Hospital there was a feeling of numbness

in her right foot. A few days later the foot became swollen and painful, so that she could not move her toes. One week later a process like that in her right foot began in her left foot and continued to grow worse while the right improved considerably. A few days before entering the hospital her right hand became affected. On admission her temperature, pulse and respirations were normal and the systolic blood pressure was 154 mm Hg and the diastolic 98 mm Hg.

The patient was a pale, poorly nourished woman who lay quietly in bed. The mucous membranes showed marked pallor. There was a slight lateral nystagmus and a fine tremor in the protruded tongue. The heart and lungs were normal on physical examination. No masses could be palpated in the abdomen, which was scaphoid. Pelvic and rectal examination revealed nothing of significance. The lymph nodes over the body were palpable, but were not tender. Reflexes in the extremities were somewhat diminished and the abdominal responses were lacking. No clonus or Babinski signs could be elicited. There was a loss of tactile sensibility over the distribution of the right ulnar nerve and an inability to extend fully the fourth and fifth fingers of the left hand. The blood studies showed 75 per cent hemoglobin (Sahli), 3.9 million erythrocytes, 25,700 leukocytes with 22 per cent neutrophils, 72 per cent eosinophiles and six per cent lymphocytes and a negative Wassermann reaction. She had a blood sugar of 87 per cent, a blood urea N of 14.5 mg per cent, and a blood creatinine of 1.2 mg per cent. The urine was clear, amber, and acid, had a specific gravity of 1.030 and contained a trace of albumin, a few white cells and occasional hyaline casts. A specimen of stool contained occult blood but no parasitic ova. A study of the spinal fluid revealed no abnormal findings and roentgenograms of her chest showed no signs of disease.

A tentative diagnosis of trichiniasis was made because of symptoms and eosinophilia and a biopsy was performed. The tissue from the gastrocnemius muscle showed no trichinae, but the small arteries showed the typical alterations seen in periarteritis nodosa. There was marked edema and infiltration of the vessel wall by large numbers of eosinophiles and plasma cells together with leukocytes. This inflammatory reaction extended well out into surrounding tissue. There was extensive necrosis of the media, and this necrotic zone was surrounded by a palisade of large mononuclear cells containing large vesicular nuclei and abundant cytoplasm.

During the first month in the hospital the patient improved somewhat, but the pain in her arms and legs persisted. There had been no elevation of temperature.

On the first day of October it was noted that the patient was drowsy. She did not respond to questions and it was thought that she had a mild

convulsive seizure. There was a paralysis of the right leg and the systolic blood pressure rose abruptly to 170 mm Hg and the diastolic to 124 mm Hg. A blood sugar determination showed 123 mg. per cent. A blood culture remained sterile. Two days later she was greatly improved but complained of "seeing double." An ophthalmological examination made by Dr. George Meyer revealed a diplopia. The pupils reacted satisfactorily and the ocular tension was normal. The only abnormal finding on ophthalmoscopic examination was a slight elevation of the nerve heads. Two days later Dr. J. S. Shipman noted hemorrhage in the retina slightly below and to the left of the optic disc. There was definitely more elevation of the nerve heads than present two days previously.

During the next 30 days the patient recovered from her stupor, the diplopia disappeared and she regained the ability to move her left leg slightly. On December 15th, fresh groups of hemorrhages were found in the retinae, but the patient complained of nothing more than persistent pains in her arms and legs. She lapsed into coma suddenly on December 23rd. The breathing was deep and irregular and was interrupted by short periods of apnea. The right pupil was widely dilated and both failed to respond to light stimulation. The right side of the face was paralyzed and the right arm and leg were flaccid. The systolic blood pressure again rose rapidly to 210 mm. Hg with diastolic to 112 mm Hg and the pulse increased to 88 per minute. On the morning of December 24, 1932, she died. The clinical diagnosis was periarteritis nodosa and right cerebral hemorrhage.

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CHAPTER LII

THROMBOANGIITIS OBLITERANS

By LEO BUEGER M D

CLINICAL CONCEPT

In the year 1908¹ the appellation thromboangitis obliterans at this author's suggestion became a neologism for the vascular affection subsequently denominated Buerger's Disease by the medical profession. Oddly enough young adults between the ages of 20 and 40 years are the most conspicuous and frequent sufferers and it is because a gangrenous complication may begin in these early years that the denotations *presenile* and *juvenile gangrene* have been frequently employed. In one class of cases there are rather characteristic attacks of ischemia. The patients complain of vague indefinitely localized pains in the foot in the calf of the leg or in the toes and particularly of a sense of numbness or coldness whenever the weather is cold inclement and otherwise unfavorable.

Upon examination we observe that one or both feet are blanched in some almost cadaveric in appearance when horizontally placed or elevated often cold to the touch and that neither the *dorsalis pedis* the posterior tibial or even the popliteal artery pulsates. When the foot becomes warm some color gradually returns. Some of those affected complain of rheumatic pains in the vitiated and impaired leg others are able to walk but a short distance before the advent of paroxysmal shooting cramplike pains in the calf of the leg ankle or foot makes it imperative for them to stop short in their walk. Many indeed most give such peculiar and distinctive features of *intermittent claudication*. After months—or in some cases even years have elapsed—trophic disturbances make their appearance.

It is at this stage that another rather unique manifestation is apt to be conspicuous one which gives the foot the appearance of redness or rubor oft mistaken for erythromelalgia. In the pendent or depressed position a bright red blush of the toes in the anterior part of the foot comes

on rather rapidly, extending in some cases to the ankle or over the leg. Soon a blister, hemorrhagic bleb, or ulcer develops, customarily near the tip of one of the toes, usually on the big toe, frequently under the nail; and, when this condition ensues the local pain becomes intense. Such "trophic disturbances" may at times make little progress and extend barely at all, but may last for months; sometimes, however, the skin in the neighborhood shows cyanotic discoloration, and dry gangrene of the whole toe is an early eventuality.

The left leg is usually the first to become affected, although both limbs may show vascular disturbances almost simultaneously; and, when such is the case, the trophic changes, the ischemia or the reddening may give rise to a symptom complex or syndrome often mistaken for Raynaud's disease. In short, after longer or shorter periods, characterized by pain, coldness of the feet, ischemia, intermittent claudication, and erythromelalgic symptoms, evidence of trophic disturbances, cutaneous defects and ulcers appear which may finally pass over into a condition of dry gangrene.

CLINICOPATHOLOGICAL ACCEPTATION

Asked to formulate a general clinicopathological notion of thromboangitis obliterans a theory and analogy could thus be formulated: Imagine a patient seeking relief for acutely swollen superficial veins of the lower or upper extremities, of sudden advent, and with all the manifestations of an acute thrombophlebitis. Imagine this process involving a considerable portion of the distal territory of the internal saphenous vein, followed by abatement of symptoms, and consequent resolution or healing. You would be in no doubt as to the habitual pathological alterations nor as to the usual clinical course of the condition, though your apprehension and estimation of the etiology would in most instances, at least, be obscure.

Transfer this picture to the deeper vascular system, over the distribution of the external and internal plantar arteries and veins, the dorsalis pedis, anterior tibial, posterior tibial, the peroneal, popliteal and femoral arteries and veins—more rarely in spermatic, cerebral, ocular, coronary, renal, pulmonary, facial, or mesenteric vessels—occasionally, with lesions in territories where objective apprehension of vascular occlusion itself is obscure—and you will be depicting to yourselves, what corresponds to

the author's assumption of the pathological process in the disease, *thromboangiitis obliterans* (Buerger's disease). Here, too, we postulate an acute inflammatory with a thrombotic lesion, but one involving deeply situated arteries or veins, or both, as the initial stage of the structural deviations from normal.

Doubtless many of you have seen cases of migrating phlebitis in patients who are heavy smokers, or without ascertainable provocation, where the territory of the saphenous vein or other large superficial vein becomes occluded, often tender, and, where the differential diagnosis between migrating phlebitis of what may be termed a "bland type" and migrating phlebitis associated with and characteristic of thromboangiitis obliterans should be made. If we excise a portion of the vein in thrombophlebitis of the bland type, we find, it is true, slight changes in the media, but an occlusive thrombus that presents no characteristic lesions. In such cases we are dealing with thrombosis alone, superimposed upon vessels that are damaged by various influences, tobacco or other causes. *In thromboangiitis, however, when migrating phlebitis occurs, certain specific architectural changes can regularly be diagnosed and found under the microscope.* That something else must call forth or evoke such remarkable structural complexes seems unquestionably true.

In arteriosclerosis, too, thrombotic lesions occur when a so-called key-stone clot closes the last remnant of the lumen of a partially narrowed vessel. But in such a clot the typical lesions of thromboangiitis are absent.

Whereas, the patient afflicted with an inflammatory and thrombotic lesion of the superficial veins presents objective signs easy of recognition, the patient suffering from thromboangiitis obliterans in its earlier stages may offer no objective evidences suggestive of the true nature, or of the site of the lesion.

It is the interference with the circulatory conditions of the limbs brought about by the extensive occlusive process that is responsible for most of the clinical manifestations of thromboangiitis obliterans, so that it may be correctly said that patients afflicted with thromboangiitis obliterans do not suffer so much from the disease itself as from the disastrous occlusive thrombosis which **signalizes** Nature's method of healing a vascular lesion that has long since disappeared.

PATHOLOGICAL CONCEPT

In the formulation of the writer's concept of thromboangiitis obliterans he postulates that pathological lesions in either deep arteries and veins or in both, or in superficial veins, more especially of the extremities, of primarily inflammatory nature, occur in respect to time in wholly fortuitous manner, and, in a spatial sense over segments of arteries or veins without essential law abiding continuity or progressiveness of direction. Because of a tendency to recurrences of similar lesions, capable of embracing continuous or discontinuous vascular domains of considerable extent large territories may become involved.

At the onset one coat alone is apparently rarely, if ever, diseased, but, as far as is determinable, almost simultaneously all coats of the affected vessel are inflamed. Immediately thereafter red thrombosis ensues although at times the inciting agent provokes partial thromboses of more restricted extent, then follows a resorptive replacement and proliferative process in the clot tending to organization; in this, there are developed certain characteristic signs of abortive attempts at capillarization, deviating in architecture from the normal, and productive of characteristic giant cell foci; then passing over into stages of connective tissue replacement, which finally yield occlusive and fibrotic masses not indistinguishable from the tissue elaborated by noninflammatory substitution of bland clots or organization, leaving vascularization of adventitia and media and perivascular fibrosis as permanent effects.

However characteristic these pictures may be, they may and usually are associated elsewhere with other intrinsic lesions of the mural layers, as well as extrinsic obliterating process, *viz.*, the development of secondary intimal degenerative lesions and elastic fiber formation within the previously affected, occluded and fibrosed vessels; or, and, secondary intimal sclerosis in patent arteries when most of them, however, are unaffected; and, the superimposition of stagnation, accretion and bland clots upon those segments already filled with the specific characteristic clots; or, and, by virtue of the impaired circulatory conditions, the appearance and subsequent transformation by organization, of stagnation, static or even infective types of thrombi, independent in origin of the primary disease, but associated with conditions easily explained upon the basis of purely local events in the territory supplied or with deranged circulation

It is concomitant nonspecific bland thrombotic and sclerotic intramural vascular changes which may be misleading to the pathologist for if they alone are examined or if no others are available for study grave doubts will arise as to the applicability and dependability of the pathological criteria just laid down and which constitute the essence of this vascular malady

With the descriptive appellation thromboangitis obliterans proposed by the writer in 1908 it was intended to give a concise designation to a pathological entity one in which emphasis was made on the coincident although not necessarily coequal importance of vascular inflammation and occlusive thrombosis as comprising the essential lesions. When applied at that time to a certain group of cases with characteristic alterations in extensive vascular domains and with many symptomatic features in common clinical and pathological data then available although numerically large were not drawn from sources sufficiently varied in geographic distribution to confirm the suspicion already then entertained that other types of inflammatory and thrombotic lesions clinically simulating thromboangitis obliterans would eventually be recognized in addition to arteritis complicating infectious disease and trauma syphilitic and tuberculous lesions and the well known periarteritis nodosa. Indeed there has accumulated in the literature of the last ten years a mass of data the interpretation of which has tended to make confusion worse confounded there have been offered many different conceptions as to the pathogenesis of this disease.

Wherever the view of an investigator or commentator has been at variance with the pathological concept set forth above the case or cases or material under consideration *did not belong to the group to which the medical profession has given the name Buerger's disease*. Thromboangitis obliterans (Buerger) is a pathological but not a clinical entity in the formal sense. The clinical course *in toto* rather than over a short period of its existence often furnishes adequate data for diagnosis. A presumptive conclusion may be made certain if pathological tissue in the form of material derived through ablation of a member or through excision of inflamed superficial veins be available.

OTHER THEORIES OF PATHOGENESIS

Until specific disease producing agents in the form of microorganisms or viruses will have been discovered for different types of arterial or

venous lesions attended with histological evidences of inflammation the great variety of interpretations now offered will continue without prospect of abatement and perhaps will be modified only in the sense of an increase in number and degree of complexity rather than of simplification and clarity. The pathologist is confronted here with a situation quite analogous to that which still obtains in the solution of the nature of rheumatic lesions.

If the pathological criteria given above are adhered to very closely it will be possible forthwith to exclude from consideration as wholly inapplicable and inappropriate the following theories whose justification lies only in the availability of naught but basically different morphological material. This has often been misinterpreted because of easily explicable and nonessential resemblances with some lesions of thromboangitis obliterans. The inapt identification of alterations of thromboangitis obliterans with certain intimal and thrombotic processes has led to further uncertainty. The lesions to which erroneous explanations have been given are those secondary to the specific alterations of thromboangitis obliterans and which in their architectural configuration are almost identical with similar changes of other types of diseased vessels. *Unfortunately, these have been fallaciously accorded the dignity of intrinsicity by many confused commentators.* Thus the following notions may be rejected as wholly incongruous irreconcilable and inadmissible.

1 Proliferation of the intima (*à* Winiwarter) or *endarteritis obliterans*.

2 Encroachment by the thickened intima on the lumen by reason of *superabundance of elastic fibers arteritis elastica* (Walonski).

3 *Stenosis of small blood vessels* by proliferating intimal thickening made up of elastoblasts and their products *i. e.* elastic membranes secondary thrombosis may be superadded or not *telangiostenosis* (Krompecher).

4 Either a *fibroplastic hyperplasia* of the subendothelial connective tissue stratum with media intact (*à*) an *endarteritis* with new formation of intimal cushions without thrombus formation or an inflammatory infiltration followed by radiate vascularization from all sides and formation of a vascular blastema an *acute arteritis* or *plebitis* also independent of and without thrombosis.

5 A productive *endarteritis* an *endovastic* (endovascular) swelling not primary but *consequent upon exogenous traumatic influence such as cold* (Gruber).

6 *Focal, intensive narrowing or closure of arterial lumina by multiple intimal cushions and also by secondary thrombosis. Primary lesion is a fibrinoid necrosis of the intima* the lesions in the smaller arteries of the type of periarteritis nodosa (Jager?)

7 Karsner³ suggests this classification of arteritis

Acute Aliterative (degenerative) necrotizing exudative vegetative (thromboarteritis) proliferative and organizing

Chronic—combinations of Intimal medial and adventitial

T A O would fall into the group primary acute thromboarteritis followed by a stage of organizing arteritis

ENIGMA OF VASCULAR DISEASE

Certain more readily understandable vascular lesions for which adequate or satisfactory causal explanations are at hand need not engage attention. Thromboangitis obliterans however belongs to those whose etiology, morphologic significance and nature of interpretation still offer uncertainty to the student. Thus thromboangitis obliterans presents a fertile theme for audacious theorizing and futile sophism.

In this discussion the writer is not concerned with the question of vascular lesions due to such processes as Athero and arteriosclerosis thromboses of static hydrodynamic and cardiac origin arteritis with embolism thrombosis as a sequence of trauma and pressure (by crutches cervical rib tumor or aneurysm) arteritis directly induced by contiguous infection or definitely attributable to a coexisting infectious malady traumatic spasm with or without thrombosis tuberculosis and syphilis and thrombosis complicating wounds and foreign bodies.

For an understanding of inflammatory vascular disease of the type thromboangitis obliterans (Buerger) the mode of origin must be viewed in the light of the following fundamental concepts

1 The reticulo endothelial system (R E S) and the endothelial components of the vessels as a part of this system in their role as cellular carriers of immunity

2 The hypothesis of activation of the endothelium

3 The theory ascribing peculiarities of the vascular lesions to an altered state of reactivity of the microorganism. In a view supporting the presumption that the tissue changes are allergic or hyperergic products

4 The doctrine of direct causal relationship. That postulating a specification of the disease agent in the production of characteristic histologic structures of the malady

Since the ultimate criterion in the evaluation of any research is its practical application this query naturally is justified. Whether do these scientific problems lead?

The unitarian aspect, as it applies to the theme has two phases.

First, the necessity for correct recognition and grouping of non-related vascular disease and diagnosis—and these desiderata, the author has tried to facilitate by indicating the general principles and prerequisites for classification and

Second, the fact that an understanding of the *modus operandi* implied by the four theories may bear fruit in prophylaxis as well as therapy.

The path to be pursued will be self-evident in each case depending upon whether the mechanism be: A participation of the endothelium as part of the mesenchyme, in the defensive processes; an aberrant activation of the endothelium with consequent tendency to thrombosis; an acquisition of hypersensitivity on the part of the vascular tissues; or, finally a specific reaction to specific agents.

If the first two viewpoints should find scientific substantiation and the morphologic aspects of the immune process lead to disadvantageous products in vascular territories involved the future may promise methods such as that used in *experimental blockade* but as a prophylactic; or, if the hypothesis of acquired sensitivity triumphs as the explanation of existing arterial lesions methods directed towards and based on the principle of *desensitization* should engage future endeavors; and finally if the correspondence between disease-producing factor and the type of lesion is paramount the search for the offending microorganism or virus should continue without abatement.

Viewed in the light of special, functional and altered reactivity the endothelium of the vessels in particular, and their other mesenchymal constituents in general, should be accorded especial significance in an appraisal and classification of diseases of more or less chronic course.

Even though the viewpoints of various schools of pathologists and immunologists are often discordant, there are certain fundamental concepts that should be taken into account by clinicians even though universal agreement in many mooted questions has not as yet been realized.

1. As part of the reticulo-endothelial system* the endothelium of peripheral vessels is believed by some to share in its properties. Among

* Reticulo-endothelial system will be abbreviated as R. E. S.

these are A function of storage, as evidenced by deposition of injected vital stains in special cells of the liver, spleen and bone marrow, and even in the endothelia of larger arteries and veins, and also as manifested by an enhancement of capacity for reaction or sensitization Siegmund has been convinced by results of experiments, that after preliminary preparation or sensitization with indifferent proteins, a subsequent bacterial injection was effective in evoking a heightened response of the endothelium, with an elimination of fibrin and the development of local conditions resulting in thrombosis Similar vascular reactions are said to occur in scarlet fever, sepsis and many other infections

2 A Dietrich too, pursuing these avenues of research and observation, has offered the concept of acquired preparedness, tendency or proclivity to thrombosis (*Thrombobereitschaft*) as indicating a heightening of endothelial function in vessels and endocardium This acquired property is said to be an altered reactivity Then followed as a logical conclusion, the opinion that the reactions of the vascular endothelium afford the basis for thrombotic depositions or, put in another way, led to the inference that an alteration of the normal relation between the blood and the vascular wall gives rise to the fundamental factors inciting thrombosis

3 Of late, increasing attention has been accorded to the significance of histological investigations and experimental researches on allergic or more correctly, *hypereirgic* inflammation Indeed, certain rheumatic lesions, those of periarteritis nodosa and of other affections have been relegated to this category Thus, it has been found (Klinge⁴ & Metz, Swift,⁵ Derick) that repeated injections of bacteria and proteins may cause certain transformations in the state of reactivity of the animal organism, that are expressed in a *heightened susceptibility* to small doses of the same poisons and in an intensification of organic or structural injury The conclusion seemed warranted that the process of surmounting certain protein intoxications and bacterial infections brings in its wake a heightened susceptibility to the corresponding offending agency

In consonance with this viewpoint, generalized damage of the mesenchyme develops, with heightened proclivity towards inflammation and in consequence, of recurring infectious action In the rheumatic state this has been ascribed by some to the effects of streptococci The primary and essential organic substrate is described as a focal fibrinoid swelling of the connective tissue with chemical metamorphosis of the ground substance, and then the development of a characteristic granulomata The Aschoff nodules in the heart and cushionlike intimal thickenings in vessels may be cited as examples

Insofar as the hyperergic or allergic hypothesis may apply to vascular disease the author is in accord with those authorities who do not wish to conform to this new fashion in medicine. The assignment of the histologic picture of thromboangitis (Buerger) into groups in which morphologic alterations are attributed to an allergic *modus operandi* just because a similarity may exist between some of the lesions of one disease with those of another is based on fallacious inference. Not only have the nonspecific and secondary structural alterations of thromboangitis obliterans been given erroneous significance as hyperergic products but there are eminent pathologists too who doubt the validity of an allergic interpretation in any or all forms of vascular disease.

The author's own studies of peripheral vascular disease have established the conviction that the interpolation of another factor that of heightened reactivity hyperergic or allergic in conditioning the products of mesenchymal reaction be they vascular lesions of thromboangitis obliterans or of periarteritis nodosa or be they Aschoff nodules or similar lesions about the joints brings the solution as to causal agency in these diseases not one iota nearer. Indeed such authorities as Aschoff⁹ & Griffo¹⁰ and Lubarsch reject the allergic hypothesis. Fahr^{10, 11} goes so far as to maintain that the rheumatic nodules are specific products of determining significance for the disease and that in their presence the diagnosis rheumatic granulomatosis can be made without further information regarding the case just as diagnosticians are ordinarily warranted in recognizing tuberculosis or lymphogranulomatosis upon the basis of a histologic preparation.

Exceedingly unfortunate is the present trend which attributes an allergic or hyperergic nature to a particular lesion in a widening list of diseases for there is thus awakened a suggestion of finality as if a solution of causality had been attained with the implication that no further search for the disease producing agent is required.

Evaluation of significance of vascular lesions must be made upon the basis of the following queries

- (a) Are local causes for vascular lesions discernible or ascertainable?
- (b) Do the distribution and wide separation of affected regions indicate a cause of systemic nature?

1. Is a given morphological development in arteries or veins the reflection of a susceptibility of certain parts of the mesenchymal system

or of an organ system to exogenic noxae in microbial or virus form or to their toxins or endotoxins or to an exogenous or endogenous toxin alone?

2 Are the character and the circumstances attending the appearance of certain morphological responses indicative of acquired hyperergic state of reactivity of the tissues and will such theory satisfy all questions as to origin?

3 Is there present a primary (in the sense of prior) alterative degenerative or decrescent lesion uncomplicated by or followed by inflammatory changes or can mechanical hydrostatic or endogenous chemical agencies account for the picture?

4 *Are the alterations in their typical form and manner of evolution so characteristic as to arouse the strong suspicion of specificity in causal connection with some organism or virus?*

It would be evidence of an unfortunate and purposeless freak of Nature if it were to become established that the endothelium of larger vessels could manifest the same active participation in the bodily defence mechanism as does the R. E. S. in the spleen and liver *and were it to respond so intensively to noxae as to succumb together with its structurally conjoined vascular components by virtue of permanent alteration and were it in this performance to compromise the integrity of the affected vessels and lose its primary local function*

Strange to say pathologists and research scholars from equally authoritative schools entertain conflicting views. One of these would have the vascular endothelium altered in infections and capable of engendering thrombosis the other categorically denies the soundness of the observations upon which the hyperactivity of the endothelium is implicated.

With Graff Aschoff and others it is perhaps best to regard Aschoff nodules in cardiac muscle of cases of articular rheumatism as reaction products of an infection as a manifestation bearing the same relation to the offending organism or virus as that which exists between the tubercle and the bacillus of tuberculosis.

To conceive of certain vascular lesions notably thromboangitis obliterans (Buerger) as allergic or hyperergic brings no clarity into the existing explanations of the origin of these manifestations. But to dispute the existence of a state of sensitivity in the vascular system would be tantamount to negating the *sine qua non* of a constitutional and dispositional morphological substratum which must needs preexist in those

susceptible to one or another malady. To infer however that the hyperergic state offers a complete and satisfactory solution of the nature of the lesions *and to reject* the likelihood of a disease producing agency would be presumptive in the extreme.

However enticing it may be to make generalizations applicable to the human body on the basis of experimentally induced lesions in the last resort the reasonable conclusions based on comparative clinical and *pathologic data should be allowed to prevail*.

A wide experience with both phases of information leads the author to these conclusions:

That the relatively high clinical incidence of venous thrombosis and a consideration of whatever is acceptable from available experimentation would justify according to the vascular endothelium in this territory some participation in the origin of thrombotic process.

That this cannot as yet be affirmed of the arteries and

That the lesions of arteries ascribable to remote infectious processes or to infectious agents have a more deepseated substratum for their evolution to wit: Mostly alterative or degenerative primary changes or primary local inflammatory changes in one or more coats.

The immunobiological function of endothelium in arteries and veins in its manifestation of alteration of reactivity be it purposeful or abortive may lead to states of morphologic mutation quite incompatible with physiological and biological destinies.

If an activation of endothelium as the result of the absorption of antigens or toxins of general or local infections is postulated thrombosis as a by product may disastrously affect the integrity of the circulatory avenues. If the theory is correct then a heightening of function—purposeful in a general teleological and immunobiological sense—must bring about devastating results in anatomic structure. In the light of the critical attitude of authorities of note (exemplified by the school of Aschoff) towards the admissibility of such a role for the endothelium of the vessels—outside of the capillaries the splenic and liver reticulum and other organs—the abortiveness of purpose implied by such participation of activities of the mesenchyme must weigh heavily against the theory.

More general concordance of views may be expected here after continued inquisitive scrutiny into the association of infectious with these endothelial responses. With intramural alterative and degenerative lesions as a first stage in vascular inflammation with so-called hyperergic

structural products or, finally with *specific types of architectural reactions*. *This much is certain, that neither focal infections, nor general infections or infectious diseases, seem to have any causal connection with that type of arterial and venous lesion which is pathognomonic of thromboangitis (Buerger)*

However satisfactory the clarification of basic laws governing morphological tissue responses to and in the immunobiologic mechanism may become in the future there is sufficient reason for a scrupulous delimitation of the category T A O* (Buerger). Nor should the pathologist be led into error by the effects of such influences on the tissue substratum of the vascular system as are wholly disparate. Such other lesions appear clinically and anatomically either as the very first involvement of arteries and veins in a given case or as complicating extrinsic processes.

Observational science both clinical and experimental has established a sufficient basis for the assumption that arterial disease of occlusive nature and of even more widespread distribution than ordinarily seen in T A O may be closely associated clinically with states indicating the possibility of absorption of novae of infectious processes or the action of organisms of unknown derivation. In such the pathological picture differs as does also the usual clinical course from that of T A O.

A variety of lesions is elaborated in the vessels during the rather long clinical course of thromboangitis obliterans. *There is but one specific type of lesion whose existence, speaking absolutely, is an essential prerequisite for the application of the proposed special designation* in actuality and for practical purposes its existence may be predicated also inferentially. Coincidentally shortly after or slowly over months and years there may develop concomitant alterations in other arteries and veins either in spatial continuity or remote from the original affected sites and capable of evolving a great variety of structural deviations from the type lesions in the vessels especially in arteries. Some are the results of thrombotic occlusion of a secondary or complicating variety not conforming in architectural details to the histologic manifestations of the malady *per se*, others are intramural and endomural changes dependent upon coexisting unrelated diseases or accidental morbid interurrences others also mural often intimal are the tissue expressions of altered local circulatory states repeated vasospasm of long duration abnormal hemo-

* T A O used as abbreviation for thromboangitis obliterans

dynamic conditions in limbs already implicated by the primary arterial lesion and subject to circulatory, metabolic and even vegetative nerve derangements indeed even elastoid mutations in certain coats and pictures simulating arteriosclerosis may be created

Such changes of merely subsidiary import—alterations not to be misjudged for the inalienable qualities inherent in vascular affection—may however in certain cases and by virtue of the large spatial extent of their occupation with involvement of territories greater than those of the initial disease offer material to the pathologist that is misleading and cause perplexity in the interpretation of the nature of the original morbid process

The elaboration in arteries and veins of anatomical end pictures of great similarity but of different origin the coincidence of intraluminal thrombosis and organization thereof with intraparietal lesions modified by the clot formation the occurrence of characteristic mural inflammatory infiltrations and concomitant pathognomonic focal lesions in the clot of T A O the inaccessibility of initial intramascular changes in most cases all this must needs give room for considerable divergent interpretation

It is understandable therefore that a great part of the pathological material made available thus far has been misconstrued and erroneously cloaked with causal significance and that inferences have been based on lesions of purely accidental or adventitious nature founded on a mere coincidence of time or on *changes secondarily conditioned* by factors not intrinsic in the morbid process *per se*

Conceptual standards prerequisite for the use of the term thromboangitis obliterans (Buerger) must be firmly established in order to attain clarity and understanding of the complexities of this as well as of other vascular diseases

A descriptive appellation such as that proposed by the writer one naming three particular attributes with the implication that their presence is the essence of the morbid process but without necessary exclusion of other qualities and one emphasizing the existence of inflammation by the designation angitis and occlusive thrombosis by the terms thrombo and obliterans—such appellation must obviously by virtue of its inherent conciseness give room for inclusion by others of some mor

bid processes possessed of these but other unnamed essential characteristics

By a generous tribute of the medical profession the requisite narrowing and restriction of the connotations of the above mentioned term have been partially accomplished in the addition of the qualifying agnominal surname of the original proponent of this designation (Buerger)

Inadequate for the inference that a given case belongs to the group thromboangitis obliterans (Buerger) as a pathological entity are circumstances and concatenated clinicopathological findings such as follow

1 *Clinical features alone* without phenomena indicating preexistence or concomitance of phlebitis of superficial veins or without histological confirmation by vein biopsy

2 *Absence of corroborating data of histologic structural nature* e. g.

When in specimens derived from autopsy or ablation of parts of or of a whole member evidence of existing or preexisting diffuse inflammation of all coats of arteries or veins with periarterial adhesions or fibrosis is unavailable or

When no acute inflammatory lesions of superficial veins or intermediate stages in the organization of previous thrombosis with residual signs of typical military giant cell foci can be detected or

When there is no evidence of previous inflammation the vessels exhibiting only organizing or organized and canalized thrombotic occluding tissue *unless* however the obliterating masses and concomitant mural alterations are of such type as to be congruent with the end (healed) stages of thromboangitis obliterans and occur in individuals whose history furnishes the missing requisite criteria such as indications of the occurrence of previous migrating phlebitis or

When the lesions are wrought other than those attributable to athero and arteriosclerosis even if the decrescent changes are accompanied by occlusive thrombi simulating those of bland stagnation or accretion thrombosis seen in thromboangitis obliterans or

When endarterial hypertrophy with or without so-called fibrinoid degeneration or other type of intramural vascular alternative process is the chief precursor or is demonstrably associated with the organizing clots or

When intense subintimal and intimal corrugating hypertrophies with or without conspicuous elastic tissue formation appear to be the lesion

antedating thrombosis and when such a picture is independent of or related in time sense with extraordinary exposure to hypothermia or ordinarily intolerable environmental and meteorological influences or

When the discoverable manifestations of acute venous or arterial inflammation with occlusive thrombosis are directly associated by coincidence of time relation with an acute infectious disease or if localized in and restricted to regions previously engaged in or still involved by a local acute inflammatory process of infectious type or

When in the presence of degenerative focal or even diffuse inflammatory vascular lesions or such in stages of resorption and regression but attended with thrombosis of rather limited extent *a direct spatial relation can be established between the site of at least a part of the pathological alterations and certain external conditions and circumstances*, such as continuous (by tumor or cervical rib) or oft repeated mechanical injury or abnormal pressure (crutches) against the affected vessel (traumatic arteritis) or

When in the larger vessels of the extremities the prerequisites laid down are not forthcoming and when smaller arteries over wide distribution exhibit lesions most nearly resembling those of *periarteritis nodosa* or

When at whatever site available for examination none other than bland thrombosis in varying stages of evolution and transformation can be found (*angiothrombosis of unknown cause*) and also wherever adequate explanation for the lesions is to be found in the deranged function of the cardiac pump, circulatory failure, embolism initiating thrombosis, be these sequelae or complications of an operation or occurring in course of infection or systemic disease. *In all these the diagnosis of thromboangitis obliterans (Buerger) as a pathological entity is not warranted*

CLINICAL AMPLIFICATION

Reported historical narrative descriptive investigative and procedural factual data have accumulated to such an extent in the literature that it would be supererogatory to reiterate and duplicate findings of others. Here are cited and interpolated case records which may fill lacunae and insufficiencies of experience. They will appositely emphasize the denotative and implicative import of their introductory captions

UNIVERSALITY OF LESIONS OF T A O

From the clinical viewpoint it is erroneous to restrict the pathological designation to those clinical syndromes in which little doubt as to the diagnosis T A O arises to those with the characteristic migrating phlebitis and to those in which microscopic identification either of superficial veins or deep arteries and veins has given confirmation. The ubiquitous localization is here illustrated.

CEREBRAL ARTERIES AFFECTED COMPLICATING T A O ASSOCIATED WITH PERIPHERAL VASCULAR INVOLVEMENT Lesions of cerebral vessels although not always characteristic of T A O occur in persons free from syphilis hypertension diabetes or other recognizable causes of cerebrovascular lesions. In 11 patients with T A O of the extremities manifesting evidences of vascular lesions of the brain out of 500 subjects affected with Buerger's disease the symptoms presented have been Hemiplegia before the onset of peripheral vascular involvement or transiently concomitantly with or after the advent of peripheral symptoms confusion disorientation aphasia loss of memory of temporary duration. The cerebral affection may outweigh in importance the usual vascular lesions of the limbs^{12 15}

The literature affords reports of 23 cases. In 11 of those observed at Mayo Clinic (two per cent of a group of 500) the ages were from 29 to 52. In most the cerebral complications followed the onset of the peripheral disease but cerebral lesions preceded peripheral symptoms in three instances. Hemiplegia was present 2 1 and 14 years before the onset of the peripheral vascular disease. Hence we must suspect T A O in cases of cerebral vascular disease of obscure causation.

INVOLVEMENT OF PULMONARY ARTERIES In the literature are six cases suggesting T A O of the lung arteries without affection of the peripheral arteries. A case observed at the Mayo Clinic is reported showing at necropsy Thrombosis of pulmonary arteries infarction of lung and thrombosis of right iliac artery. Microscopic examination of pulmonary arteries is believed to warrant the diagnosis of T A O¹⁸

INVOLVEMENT OF ABDOMINAL ARTERIES There are cases recorded in the literature three of the 500 studied at the Mayo Clinic.

INVOLVEMENT OF SPERMATIC ARTERIES Two are found in the literature¹⁸ The lesions resembled tuberculosis of the epididymis. Buerger¹⁶ refers to one case in his book on circulatory disorders.

INVOLVEMENT OF RETINAL ARTERIES ASSOCIATED WITH T A O OF LEGS Vascular alterations in brain and fundi are reported. Sudden impairment of vision is mentioned.^{1 18}

QUESTIONABLE NATURE OF LESIONS INVOLVING EXTRAPERIPHERAL ARTERIES In the few autopsy records available, the microscopic examination of visceral arteries disclosed the presence of pure degenerative lesions whereas the peripheral vessels exhibited the typical inflammatory picture of T A O. Thrombosis is common.

An exception is the instance of the T A O of pulmonary artery which revealed inflammatory changes.

Most reports of changes in visceral arteries describe atherosclerosis.

T A O OF CORONARY ARTERIES OF HEART A man, aged 35, succumbing to acute respiratory infection who had had T A O of both lower members without cardiac disease, disclosed at autopsy a combined picture of acute T A O and arteriosclerosis of the coronary artery, and also organized thrombi. In the opinion of the author¹⁹ the coronary sclerosis was favored or resulted from an inflammatory lesion.

Typical 'acute alterations' of T A O have been found in the descending branch of the left coronary artery with typical milium abscesses in a patient who succumbed to coronary thrombosis, T A O of the peripheral vessels being present.

At the Mayo Clinic, complicating coronary arterial disease was found to be the most frequent cause of the lethal outcome in patients afflicted with T A O.

DIGITAL AND PALMAR ARTERIES W B S, male, aged 36 executive consulted the author on October 14, 1932 recounting that while in California in February a 'sore spot' appeared on the thumb of the left hand near the distal interphalangeal joint then coldness of the fingers followed by discomfort when entering and remaining in a cold room. Thereupon the index finger was similarly affected. Avers that the onset took place during a golf game and the soreness lasted six weeks.

In September, 1932, about three weeks ago another sore spot was felt over the palmar surface of the index finger, then coldness especially in lowered atmospheric environments and tendency to perspire was brought to his attention.

Examination Thumb and index fingers of left hand exhibit excessive perspiration the cutaneous circulation is sluggish there is some pallor of both fingers as compared with third, fourth, and fifth fingers. Both radial and ulnar arteries pulsate. Both dorsalis pedis pulses are absent.

October 15 1932 The lateral digital arteries of the left thumb can be felt as hard cords throughout their course from the metacarpophalangeal joint to the distal interphalangeal, they do not pulsate. Whilst the ulnar (mesial) digital artery of the index finger pulsates the radial or outer digital pulse is absent. Distinct beats are perceptible in all other digital arteries. Control palpation of corresponding digital vessels of other hand reveals adequate beats.

Recording oscillometry disclosed absence of undulations or fluctuations when transmissions were taken from the affected fingers thermometric readings with potentiometer recorded a lowering of temperature of about 4°C (7°F) over left index finger as compared to the right a similar slightly less diminution of temperature over left thumb and distal portion of the palm of left hand in situations corresponding to the root of the ischemic digits

Subsequent Course Rapid improvement over the years 1932 1933 and 1934 although extension of the occlusive process in the arteries of feet and legs did occur up to 1935 when an arrest of progress did take place

Diagnosis T A O of the arteries of the lower extremities digital arteries and palmar arch of the left hand Compare with this citation²⁰

T A O CORONARY THROMBOSIS REFLEX BONE DYSTROPHY The latter condition also known as posttraumatic osteoporosis chronic traumatic edema traumatic vasospasm Sudeck's acute atrophy of bone patchy lacunar osteoporosis hard nonpitting edema in bone osteoporosis with irregular spotty atrophy of bone in roentgenograms Associated are pain usually paroxysmal extreme sensitiveness to changes in temperature (to heat in some) or to pressure At first the temperature may be higher than on the normal side later it is often lowered Profuse sweating trophic changes are common The skin may be glossy and bluish Occasionally the joints are painful the capsules shrinking and movements become painful

This state follows even mild traumata low grade infections slight injury to nerves burns or frostbites At times disability is long continued even complete Pain may be so severe that amputation is required

Explanation Exaggeration of nutritional reflex which does not subside after having been motivated by original injury or infection becoming a self-perpetuating mechanism in which catabolic (destructive) activities are predominating (deTakats) This reflex is actuated by a chronic focus of irritability in the periphery producing continuous stimulation throughout the ordinary sensory paths to the cord with relay to lateral horn and from here efferent sympathetic impulses to tissues follow

BONE ATROPHY IN T A O D R F male aged 37 February 18 1939 Five years ago sustained a fall from a tree attributing trouble to this happening has tired feeling in left leg for over three years

November 1936 an attack of coronary thrombosis second episode February 25 1938

Late in November 1937 tried on some riding boots that were much too tight causing severe pain in left foot and when they became unbearable after some two hours the boot on the left foot and leg could be removed only with extreme difficulty Bared the foot as found as often

Hereafter swelling remained for some three days and pain discoloration and sensitivity to heat have persisted ever since

Circulatory Status Findings atypical of T A O of both legs left foot colder than right neither dorsalis pedis nor posterior tibial pulsates, popliteals small almost imperceptible oscillations diminished just below the knee

Hassermann Negative Electrocardiogram typical of coronary artery disease

Roentgenogram March 15 1939 Characteristic lesions of Sudeck's atrophy of bones of left foot

Chief Symptoms of Left Lower Member Pain especially nocturnal inability to tolerate heat vasomotor lability cyanosis and pallor extreme tenderness of all of the bones of the left foot moderate swelling of the left foot and distal part of leg

Diagnosis T A O of both lower extremities coronary thrombosis symptoms in the left leg due in the main to macular patchy reflex bone atrophy attributable to trauma described

T A O OF GASTRIC ARTERY Unmistakable lesions of T A O were recognized by the author (Buerger) microscopically in one of the branches of the gastric artery far removed from the site of an ulcer because of which extensive resection (sleeve type) had been performed

THROMBOSIS OF ARTERIES Instances of thrombotic (blind compression irritative traumatic) occlusion of vessels of the upper extremity are occasionally reported as due to an anomalous first rib they have given rise to erroneous interpretations such as of T A O²¹

ACUTE VASCULAR SPASM Traumatic spasm with manifestations not unlike those occasionally revealed by sudden thrombosis of larger veins may simulate the effect of arterial embolism or even the picture of T A O

Acute arterial spasm concurrent with contemporaneous and evoked by venous thrombosis may be responsible for gangrene²²

PNEUMATIC HAMMER DISEASE Characteristic are blanching and numbness of fingers when exposed to low temperatures The use of vibrating tools by stonecutters cobblers shoemakers and others cause these as well as Raynaud phenomena also cyanosis and nutritional changes of the fingers If complicated by thrombosis of digital arteries diagnostic differentiation from T A O may become a problem²³⁻²⁴

ARTERIOVENOUS ANEURYSM OF EXTREMITIES Confusion with disconnection because of failure to identify this typical syndrome will be avoided by recalling the usual picture A history of injury by a projectile knife thrust flying steel or glass resulting in profuse but controllable bleeding then the origination of a thrill and bruit continuous throughout the cardiac cycle large fistulae ultimately leading to dyspnea tachycardia pounding of the heart even decompensation from cardiac dilatation

Local manifestations such as edema elephantiasis difference in size of the sister limb a pulsating mass yielding thrill and bruit, dilated or pulsating veins varicosities eczema ulceration, sometimes gangrene. These offer an aggregate of distinctive traits."

RAYNAUD PHENOMENA WITH OCCLUSION OF DIGITAL ARTERIES Here a nice sense of discrimination need be invoked to make valid distinctions capable of setting this condition apart from T A O pneumatic hammer disease arteritis resulting from local or generalized infectious morbidity and toxemias cervical rib scalenus anticus syndromes and bland traumatic thrombosis of the digital arteries. These considerations flow from the recent pathological findings of T Lewis to wit:

Obstructive disease of the digital arteries manifested in two cases of intermittent spasm in which the finger tips presented the scars of small healed necroses the arterial wall presenting intimal hyperplasia the lumens conspicuously reduced or actually occluded by new cellular tissue or by recent or organized thrombus striking lesions revealed in scarred and unscarred fingers where intermittent spasm in fingers was associated with necroses thrombotic obstruction of the digital arteries was the rule the thrombi being in various stages of organization. In subjects afflicted with bilateral discoloration and necrosis of fingers and predominant lesion was thrombosis the thrombi disclosing various stages of organization. In diffuse scleroderma where attacks of discoloration of the fingers occur an occlusive disease of the digital arteries was discovered."

T A O SUPERIOR LABIAL CORONARY ARTERIES (a labialis superior) Acute onset development and abatement in a female while under observation and treatment for extensive T A O of vessels of both lower limbs and inconsiderable affection of the upper extremities.

V V housewife aged 34 consulted the author on January 27 1939 because of manifestations of typical T A O of both lower members lasting five years with bluish discoloration of left foot cyanosis and coldness in both feet extreme tenderness of right foot and for an ulcer one quarter inch in diameter at the tip of right big toe another adjacent to the nail of the fourth and a third over the tip of the little toe. Dorsalis pedis and posterior tibial pulses were bilaterally effaced right popliteal pulseless the right femoral beat small.

Subsequent Course Hospitalization then office and home ministrations followed by satisfactory improvement and healing of ulcers.

Acute Involvement of Labial Arteries About July 1 1939 annoyed by pain and slight swelling of the upper lip.

July 8 1939 there was palpable throughout the mucous surface of upper lip a cordlike hard infiltration that arose at a point one quarter inch mesial to the right lateral corner of the mouth about one third inch above the mucocutaneous margin and coursing mesially disappearing near

the philtrum This cord lying in the course of the coronary, superior labial artery (or comitative large vein) definitely indicated and reflected an inflammatory and thrombotic process in a vessel The mucous membrane and cutaneous surfaces of the lip were normal

Coincidentally pain developed in the right hand over its dorsum and also in the left palm

Treatment Injections of neoprontosil also sulfapyridine

July 13 1939 the vascular thrombosis had extended laterally In the left half of the upper lip a small fine cord is discernible on palpation, originating at a point near the nasal septum passing laterally and downward to within three-eighths inch or less of the margin of the lip then turning laterally

July 23 1939 the mesial portions of the cordlike structures are diminishing in size the lateral having progressed spatally are tender with moderate swelling of the lip

July 27 1939 induration of right coronary artery almost imperceptible a very attenuated cord remaining but a nodule still present on the left side

August 5 1939 lip is almost normal Sulfapyridine seems to have hastened recovery

T A O THROMBOSIS OF THE CAROTID ARTERY A married man 41 years old a bookkeeper, consulted Dr Clarence E Rees on May 6, 1935 complaining of a purplish discoloration of the left leg and cramps on exercise In 1932 he had cramplike pains in the left leg and an ulcer of the great toe two months later he had a 'stroke' with involvement of the left arm and face the paralysis abating in about three months but the ulcer persisting for one year Cramps in the leg were made worse by moderate exercise

In May, 1935 the left lower extremity was cold and cyanotic when dependent and cadaveric on elevation The posterior tibial and dorsalis pedis pulses were absent (both were present in the right ankle), the radial pulses were present there was a scar of a healed ulcer on the great toe

On June 10 1935 a left lumbar sympathectomy with removal of the second third and fourth ganglia was done Ulceration developed over the internal malleolus while the patient was in the hospital The patient improved and returned to work

On December 3 1936 after lifting a heavy object he experienced sudden pain in the left leg and lower posterior thigh accompanied by swelling shortly thereafter gangrene of the foot The patient was sent to the hospital On December 18 the leg was prepared for amputation for the following morning Two hours later the patient went into shock he was confused his skin became cold and clammy the pulse dropped to 56 swallowing was difficult and he was not able to talk The following day,

absence of the left carotid pulse was noted there was twitching of the right leg and weakness of the right face. The leg was amputated on December 30 1936. All symptoms cleared except the aphasia which persisted for several months and then gradually disappeared.

To this day February 2 1940 there has been no return of pulse to the left carotid which can now be palpated as a fibrous cord.

Microscopic study of the carotid has not been made but sections of vessels from the amputated leg showed the typical lesions of thromboangitis obliterans.

EQUIVOCALNESS OF OBSERVATIONAL INFORMATION

Clinical Capriciousness Supporting the view that diagnosis may be perplexing are the vagaries multifarious nature and uncertainties of symptomatology which deserve attention and elucidation being correlated and dependent upon some of the following circumstances alterations and conditioning moments

- 1 The *chronicity* of the vascular malady
- 2 The *ubiquity* of localization
- 3 The *subordinacy* of external and intrinsic mutations manifestations and physiological disorganization to the nature (inflammatory occlusive) and locality of the diseased processes
- 4 The *immediate* and *late* or *temporally remote* effects of blockage of arteries or, and veins
- 5 The *extension* of the *inflammatory lesions* to the peripheral (accompanying) nerves
- 6 The *direct* and *reflex* results of impaired and altered sympathetic nerves and of their function
- 7 The *reflexes engendered in the periphery* by virtue of vascular occlusion mural changes inclusion and irritation of ganglion cells and nerve fibers with concomitant late outbursts or outbreaks of abnormal vasoconstriction
- 8 The *gross* as well as the *indeterminable* and *latent* results of impaired nutrition
- 9 The *disintegration deterioration transformation* and *disorganization* of Arterial circulatory mechanism (centrifugal blood flow) the venous return the vasomotor rhythm and responses
- 10 The *altered resistance of tissues* the *disequilibrium* of the cell environment making cell adaptation inadequate the *cellular incapacity* to adjust itself to a *deviated disturbed* and *abnormal internal medium* as well as to *external and meteorological influences*
- 11 *Potential oxygen deficiency* exaggerated increased and aggravated in ectodermal tissues that are poorly supplied with capillaries

12 *Potential inadequacies made manifest* in organs where there are terminal blood vessels with no or poor anastomatic connections brain (cerebral vascular T A O) heart (T A O of coronary arteries) vasovisorium (blocked by acute lesions of T A O), eye (T A O of retinal vessels) kidney (rarely) skin papillae (T A O common in extremities)

13 *Associated vasospasm* With blockage of cerebral arteries of peripheral arteries with thrombophlebitis especially of larger veins etc

14 *Accentuation of clinical phenomena* due to inherent functional vasolability susceptibility to thermal and physical chemical and meteorological conditioning

15 *Circulatory disturbances in provinces* far removed from the limbs (so-called extraperipheral) yielding a multiplicity of varied indications of their vascular origin the vessels themselves escaping the application of special investigative procedures

16 *A variable, diverse sequence of occurrences*, partly in the direction of physical structural decadence degradation and deterioration in any of the domains whose blood supply has been impaired concomitant with and followed by Severe sanguineous depletion ominous anoxemia dissolution (so-called dysintegration) ²⁷ derangement disorganization of the autonomic functions or autonomic inadequacy a picturesquely diversified gamut of tissue necroses with consequential infections thrombophlebitides lymphatic lesions structural alterations of (sympathetic) autonomic nerves and even acute episodes of thrombosis in the more centrally situated still patent arteries *transforming the regional outcome from one compatible with conservation of the affected limb or part to another perhaps inconsistent with continued viability*

CLASSIFICATORY OBJECTIVES

With denotative appellative terms—corresponding accurately with incontrovertible observational data—well established and now almost universally accepted is apposite and appropriate what traits have compilations of clinical and pathological reports coordination of available investigations and critical reviews disclosed?

We have selected particular distinguishing features characteristic of the morphological deviations and divergences from normal vascular architecture of evanescent existence subject to mutation with the progress of time as of pathognomonic and determinative import endowed with the capacity of giving the most significant clues to the nature of the category that we have postulated

These are the difficulties confronting the observer frequently perplexed by multifarious clinical circumstances aspects and sequences con

fused and irresolute in his differentiation of maladies by reason of overlapping mimicry resemblances and seeming identities of objective phenomena

1 The lack of clinical criteria or standards for recognition of objective phenomena in most phases of the course of T A O

2 The paucity of antecedent conditions or prerequisites for discernment of distinctions between several of the peripheral vascular affections

3 The restricted time period of observation given to the individual physician often inadequate for the advent of salient diacritical or definitive vital indications

DISTINGUISHING TYPIFYING PECULIARITIES

1 Incidence preponderatingly in young (20 to 40 years) males

2 Usually of slow insidious onset in blood vessels of lower limbs next in frequency is the involvement of arterial distribution in the upper members

3 Characteristic histological alterations and microscopic configurations of sections of arteries or veins in the acute inflammatory phase especially and easily identifiable in excised portions of veins in state of so called migrating phlebitis

5 Unique peri and intervascular inflammation with subsequent fibrosis encircling vessels as well as nerves

6 Frequency of the development of coronary thrombosis manifestations stigmatizing the vascular disease is capable of universal distribution with a tendency not only to progress in the peripheral blood vessels arteries and veins but localizable in any domain or territory to wit In renal spermatic splenic gastric pulmonary cerebral cardiac carotid retinal suprarenal and even aorta

Adumbrant premonitory indicative appearances occurrences unforeseen unexpected happenings incite diagnostic prescience but do not permit or warrant irrefutable and unassailable diagnostic inferences namely Migrating phlebitis vasomotor disturbances in the extremities intermittent claudication before peripheral pulses are absent fissures or ulcers of fingers or toes without local indicia of causal agencies hemianopia disorientation psychic aberrations transitory or permanent hemiplegia thrombosis of a vein or artery of spermatic cord pulmonary symptoms with or without dilatation or hypertrophy of heart of unexplained origin coronary thrombosis ocular disturbances without ascertainable

etiology, and other symptoms in territories whose arteries may have become occluded with the lesions of T A O

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CHAPTER LIII

ERYTHERMALGIA (ERYTHROMELALGIA) OF THE EXTREMITIES

(A SYNDROME CHARACTERIZED BY REDNESS HEAT AND PAIN)

By EDGAR V. ALLEN, M.D.

Definition. The term *erythromelalgia* which is derived from the three Greek words *erythros* (red) *melos* (extremities) and *algos* (pain), indicates red painful extremities (S. W. Mitchell 1878). This term however is not entirely adequate because it does not denote the importance of heat. If only redness and pain were necessary for the diagnosis of *erythromelalgia* such a diagnosis could be made in many cases of *thromboangitis obliterans* or *arteriosclerosis obliterans* for in these conditions the feet are commonly red and painful.

A more descriptive term namely *erythremalgia* seems appropriate for the syndrome commonly called *erythromelalgia*. It is derived from the three Greek words *erythros* (redness) *therme* (heat) and *algos** (pain) and therefore comprehends the three important components of the syndrome. Since this new term cannot be applied to what has already been denoted as *erythromelalgia* I have enclosed the word *erythromelalgia* in quotation marks and have used the term *erythremalgia* whenever such usage seemed appropriate.

The literature relative to *erythromelalgia* is very confusing. Many cases have been reported as examples of *erythromelalgia* which bear only the slightest resemblance to the condition. Part of the confusion results from the fact that in earlier times reliable methods of determining the temperature of the skin were not available and part from the lack of a precise definition which as Lewis has pointed out was evident even

*I have used the term *erythros* to designate the discoloration observed in this syndrome. It varies widely in intensity in different cases. In appearance it varies from a dusky or cyanotic redness to a light redness. Usually it is the least remarkable of the three constituents of the syndrome. The term *therme* is used to indicate heat or excessive warmth. Although the chief attribute of this term lies in its indication of objective warmth or heat it may also express subjective warmth or heat. The term *algos* indicates pain of a nonspecific nature which is less tolerable than mere discomfort.

in Mitchell's original presentation. The literature on the subject was reviewed by Cassirer in 1912, and by May and Hillebrand in 1924. Since the latter date little of importance has been published except the reports of Brown, Lewis, and Mufson.

The condition is characterized by burning distress, involving any of the extremities, which is inseparably linked with, and entirely dependent on, elevation of the temperature of the skin of the affected parts. When the temperature of the skin is elevated to or above a certain critical level by any means, distress occurs, and when the temperature of the skin is reduced, by any means, to a point below the critical level, the distress disappears. This condition affects otherwise healthy persons who do not have any detectable organic disease of the nervous or vascular systems, and it may therefore be considered a primary disturbance.

Occasionally the syndrome may be associated with hypertension or polycythemia, and it may occur in organic neurologic or vascular disease, but under these circumstances it seems to be a secondary manifestation of the organic disease. Whether primary or secondary, however, the syndrome is essentially the same. An analogous situation holds in Raynaud's syndrome, for vasomotor symptoms similar to those observed in Raynaud's disease may occur in thromboangiitis obliterans, arterial thrombosis due to cervical rib, and in a variety of other conditions which do not warrant the designation "*Raynaud's disease*" because the vasomotor syndrome is obviously secondary to organic disease. I am not concerned here with Lewis' observation that the syndrome may involve areas other than the extremities.

PATHOLOGIC PHYSIOLOGY*

Increased Temperature of the Skin: An increase in the temperature of the affected extremity in erythralgia is invariably accompanied by distress. It makes no difference whether the increase occurs spontaneously or is induced by local application of heat, as by immersing the extremity in warm water, increasing the temperature of the environmental air, or warming the skin by direct contact with a warmed metal bar.

Of all the various disturbances occurring in erythralgia the increased temperature of the skin is the most important, and it is entirely constant. The temperature at which distress can be produced varies with

* For the purpose of clarity I have simplified this phase of the presentation and intentionally avoided detail.

different individuals and in different parts of the extremity of the same individual. It usually lies within the range from 32° to 36° C (89.8° to 96.8° F). Lewis designates the critical point, is an excellent one; it indicates the temperature at which distress occurs. With temperatures higher than this critical point the distress persists and with temperatures below this critical point the distress disappears. Lewis has justifiably objected to the intimation that increased temperature occurs in episodes indicative of vasomotor storms, for the increased temperature and hence the distress may be reasonably constant.

Vasodilation. Vasodilation is the commonest cause of the increased temperature of the skin in erythralgia. It seems to be the direct cause of the attacks of burning distress which occur spontaneously. Vasodilation, however, is only an indirect and not an integral part of the mechanism causing the distress. This is shown by the observation that distress can be induced by warming the skin of an extremity affected with erythralgia, or it can be maintained in such an extremity when the flow of blood has been brought to a standstill by inflation of a cuff about the extremity to a pressure greater than the systolic blood pressure, provided the warmth of the skin is as great as or exceeds the critical point. Evidence of vasodilation other than increased temperature of the skin is increased amplitude of arterial pulsation, the throbbing sensations that are frequently mentioned by patients, increased elimination of heat (as shown by calorimetric studies), and increased content of oxygen in the venous blood coming from the extremity.

Hydrostatic Pressure. If the temperature of the skin is just slightly below the critical point distress may be induced when the intravenous pressure is increased by placing a sphygmomanometer cuff about a proximal joint of the extremity and inflating it to a pressure about the same as the diastolic blood pressure. In addition, distress may be lessened if an extremity is elevated and accentuated if an extremity is dependent even if the temperature of the skin remains unchanged. The burning distress may be relieved by direct pressure on the skin. I cannot agree with Mufson that the fundamental cause of the distress in erythralgia is relative hypertension within the minute vessels of the skin; for, if the temperature is suitably increased distress may be induced in an extremity in which blood flow has been stopped.*

* By means of inflation of a sphygmomanometer cuff about a proximal joint

Susceptible State of the Skin: It is apparent on even superficial consideration that temperatures of the skin which almost routinely* provoke distress in patients with erythralgia have no such effect on those without erythralgia. This observation caused Lewis to describe a "sensitive state of the skin." It seems unquestionably true that, for reasons not clearly understood, the skin in erythralgia is sensitive in an unusual degree to warmth.

Vasoconstriction: In some instances there seems to be unusual vasoconstriction in the extremities between episodes of burning distress. This is shown generally by hypertension in some cases and locally by coldness and cyanosis or pallor of the skin between the episodes of burning.

NATURE OF THE DISTRESS

Mitchell's "pain of a burn," "pain of mustard," and "pain of intense sunburn," are graphic descriptions of the severity and character of the pain. The patient usually states that the distress affects the ball of his foot or the tips of his toes, or the corresponding parts of the hand. However, as one induces distress for purposes of study, it is often described vaguely by the patient as an aching, pricking, sticking, pins and needles sensation which may not be localized at all and which may extend up past the ankle or, as it becomes more severe, may reach the knee or even the hip. This type of pain is not burning until the critical level of temperature is exceeded. Moreover, it is fluctuating in type, rising in increasing waves, with shorter and shorter intervals between crests, until it passes from the sticking, pricking type of pain into a definitely burning distress. A modified form of this pricking stage may be noticed as the extremity cools below the critical temperature.

DIAGNOSIS

A diagnosis of erythralgia is justified provided there is close correlation between temperature of the skin and the distress. While there may be other manifestations, such as those mentioned in the preceding paragraphs, the dependency of distress on the temperature of the skin is characteristic and pathognomonic of erythralgia. Sensations of burning in the extremities such as are commonly noted by patients with

* A "resistant phase" has been noted in patients with erythralgia. If high temperature of the skin and distress are produced repeatedly, a transient period may be reached in which an increase in the temperature of the skin is not associated with distress.

arteriosclerosis and peripheral neuritis, for example, do not indicate erythralgia. While close questioning of an intelligent, observing patient who has noted objective absence or presence of increased warmth of the skin when burning distress occurs may allow tentative exclusion or acceptance of the diagnosis of erythralgia, the final diagnosis must be based upon objective studies.

METHODS OF STUDY

In order to demonstrate the essential relationship between skin temperature and distress, it is necessary to increase the temperature of the skin to a value at which distress occurs. This can be accomplished in several ways. (1) Reflex vasodilation can ordinarily be accomplished by means of a baker containing five or six carbon filament lamps so supported that they are about 46 cm (18 inches) above the skin of the abdomen and chest. A blanket is placed over the baker and the feet are exposed to room air. The temperature of the air within the baker usually is between 50° and 60° C (122° to 140° F). Sometimes simply wrapping the extremities in blankets will cause an adequate increase in the temperature of the skin. (2) Direct warmth can be applied by enclosing the extremity within a rough blanket tent, within which a lighted carbon filament bulb is placed. For some reason I have not had much success in producing the distress by immersing the extremity in warm water. The reason for this is not clear. A cylindrical copper bar, about 2.5 cm (1 inch) in diameter, may be warmed to the desired temperature by immersion in water and applied directly to the skin. Whenever these methods are used, distress is more easily induced when the extremity is dependent. The explanation for this is presented in the paragraph on hydrostatic pressure.

If erythralgia is present, burning distress occurs as the temperature of the skin increases. Ordinarily, burning occurs when the temperature of the skin is increased to about 32° C (89.6° F), and this burning increases in intensity as the temperature of the skin is still further increased. If the mechanism for increasing the temperature of the skin of the extremity is removed and the temperature decreases, the distress disappears. Ordinarily, the critical point of temperature varies less than 1° C (0.5° F) in repeated experiments, although different patients have somewhat divergent critical points. If distress is induced repeatedly, a

resistant phase may occur during which distress cannot be produced even though the temperature of the skin is increased satisfactorily. If the distress is proved to be dependent upon the temperature of the skin the diagnosis of erythromalgia is established. Confirmatory findings are an increase in the distress when the extremity is dependent or when the venous pressure is raised by means of a sphygmomanometer cuff and a decrease in the distress when the extremity is elevated or immersed in cold water.

REPORT OF CASES

CASE 1. A white man, a foreman of underground construction in a gold mine, aged 31 years, registered at The Mayo Clinic in September 1937. In February 1936 a falling rock had caused a chip fracture of the bone of the left great toe from which recovery was prompt. In January 1937 for a short time pain in the left great toe and foot associated with some swelling of the foot caused limping. The patient felt that the resultant distress was not the same as that which he experienced subsequently. In July 1937 this latter type of distress which will be described subsequently appeared and as a result the fragment of bone was removed from the left great toe. Relief was not experienced except while the patient was in bed.

From the time of onset in July 1937 to the time of the patient's admission to the clinic he had experienced eight attacks of distress, each of which lasted three or four days. At first only the left great toe was involved but in the last two attacks the discomfort spread to the ball of the foot and the fifth toe. This distress was described as hot, burning, throbbing, aching and pulsating in nature. It seemed to be precipitated and aggravated by work, walking or climbing. Relief was obtained constantly but transiently by rest, elevation and cold water. Some medicine which the patient believed to be sodium salicylate had not helped. Because of the distress the patient was forced into a sedentary occupation. While he was driving in Rochester he discovered that ten grains of acetyl salicylic acid (aspirin) produced prompt relief which persisted for about three days. He had noted increased surface temperature red to deep purplish discoloration and increased sweating of the foot during episodes of distress.

Physical examination and routine laboratory tests gave negative results. The peripheral arteries pulsated normally. The percentage volume of cells in the blood (hematocrit) was 53.0.

The patient lay on a bed in a room which was kept at a constant temperature, fully clothed except that his shoes were removed for 40 minutes. His socks were removed at 1:50 p. m. and he lay with his feet

exposed until 2 25 (Table I). No distress was noted. At 2 25 he sat on the edge of the bed with both feet dependent. Distress of a throbbing type involved the left first toe and the outer side of the left foot in about 25 seconds. The temperature of the left foot increased rapidly, and as it did so, 'aching', burning, and soreness occurred in the distal half of the foot. Changes in the temperature of the skin of the right foot were minimal (Table I). On a subsequent day, during an episode of spontaneous distress associated with an elevated skin temperature, the patient was given ten grains of acetylsalicylic acid by mouth. Complete relief was experienced in 20 minutes, although the skin temperature was not influenced by the drug. It was also shown that immersion of the foot in cold water gave immediate relief. Additional studies showed that vasodilation was more easily induced in the afflicted areas than elsewhere. When both feet were wrapped loosely in a blanket, within which heat was produced by a carbon filament bulb, the temperature of the skin of the left first and third toes and of the ball of the foot increased more rapidly than did that of corresponding areas of the right foot (Table II). This procedure carried out two or three days after the patient had ingested aspirin did not produce distress even though the temperature of the skin was high.

These observations seem to be important. As expected there was a close relationship between the distress and the temperature of the skin. The critical point was from about 31.0° to 32.0° C (87.8° to 89.6° F). Most surprising was the marked increase in the temperature of the skin of the left foot as a result of dependency alone, in contrast, there was very little change in the temperature of the right foot. Noteworthy also was the prompt relief following the administration of acetylsalicylic acid.

CASE 2. A man, 48 years old, was examined at the clinic in December, 1930, because of pains in his arms and chest, weakness, nervousness, poor memory, and dizziness. The value for hemoglobin was 17.8 Gm per 100 cc and the erythrocytes numbered 4.7 millions per cubic millimeter. The diagnosis was anxiety neurosis. The patient returned to the clinic in August, 1936, when the symptoms just mentioned had to a large extent disappeared. For two years he had noticed burning distress involving various areas of the skin of his right foot, chiefly the plantar surface and first toe. Reddish discoloration of the foot had also been present. The distress, which was fairly constant, was made worse by walking which also increased the discoloration and the cutaneous temperature. The patient was finally forced to walk with a cane. Relief from the distress was experienced on elevation of the foot. Immersion in cold water had not been tried.

On examination, there was an unusual redness of the skin of the face, cyanotic discoloration of the buccal mucosa, and increased reddening of the conjunctiva. The entire right foot was dusky red and obviously warmer than the left. The veins of the right foot were distended. The liver and spleen were slightly enlarged to palpation, and the heart was slightly enlarged to percussion. The blood pressure was 178/112. The value for hemoglobin was 20.9 Gm per 100 cc., and the erythrocytes numbered 5.13 millions per cubic millimeter. The percentage of cells in the whole blood (hematocrit) was 66, and the whole blood volume was 8009 cc., or 109 cc. per kilogram of body weight. The value for blood uric acid was 3.7 mg per cent. The respective temperatures of the skin of the right first, right third, left first, and left third toes in degrees centigrade were 31.9, 32.1, 27.6, and 26.8. Blood taken from a vein on the dorsum of the right foot contained 21.5 volumes of oxygen per 100 cc. (91 per cent saturation), whereas that drawn from a vein on the dorsum of the left foot contained 18.7 volumes of oxygen per 100 cc. (69.5 per cent saturation). There was roentgenologic evidence of osteoporosis of the right foot. A diagnosis of polycythemia vera and erythralgia was made.

Because of financial reasons, the patient returned to the care of his local physician, who on four occasions performed venesection. A year after the patient had been dismissed from the clinic his physician wrote that the patient no longer had distress in his right foot.

Examination of the patient and of his blood established the diagnosis of polycythemia vera. All the criteria of erythralgia were satisfied, namely, reddish discoloration, increased temperature of the skin, and the characteristic burning distress. At the clinic, the relationship between erythralgia and polycythemia has become so firmly established that polycythemia is suspected when there are symptoms suggestive of erythralgia.

Most interesting was the finding of the high concentration of oxygen in the blood taken from the vein on the dorsum of the right foot. The content of oxygen in this venous blood approached that normally found in arteries. This phenomenon was noted previously by Brown, who considered it as evidence of a high degree of vasodilation. Another explanation which occurs to us is the functioning of the arteriovenous anastomoses which normally are not functioning, or are functioning to a less degree. Such an hypothesis would help to explain the dusky redness of the skin, indicating a low oxygen content of the capillary blood while at the same time there was a high concentration of oxygen in the venous

blood. In other words blood may have been shunted directly from the arterioles to the veins.

One of the objections to accepting polycythemia as the cause of the erythralgia was the unilaterality of the latter condition. Since the disturbances in circulation resulting from polycythemia are bilateral one might reasonably expect erythralgia to be bilateral. However illogical it may seem there is in our experience a direct cause and effect relationship for a return of the blood to normal may cause the disappearance of unilateral erythralgia. It may be that one extremity has some inherent susceptibility not present in the other. Unfortunately we can only assume and not be entirely certain that in the case under discussion relief of the polycythemic state was responsible for the disappearance of the erythralgia. We see no difference between the syndrome noted in this case and that which occurs primarily except that the distress was more constant apparently because the cause of the vasodilation was persistent.

TREATMENT

The treatment of erythralgia is not uniformly successful as was observed originally by Mitchell and emphasized by Brown. It is of course important to determine whether there is any condition such as polycythemia to which erythralgia might be secondary. Under such a circumstance the treatment of the syndrome affecting the extremities would be the treatment of the condition which produces it. Surprisingly acetylsalicylic acid in amounts of as little as 0.6 Gm. (10 grains) may produce marked relief which persists for as long as several days. No adequate explanation of this is available but it is so common that we have learned to suspect erythralgia whenever patients mention marked and prolonged relief as a result of using this drug.

Mufson noted marked relief following the injection or inhalation of solutions of epinephrine *chloride*. He believed that the distress of erythralgia was a manifestation of relative hypertension in the minute vessels of the skin a condition which epinephrine relieved. I have not had enough experience with this method of treatment to justify an opinion as to its efficacy.

Some symptomatic relief may be obtained by avoiding procedures that produce vasodilation in the extremities. Residence in a moderate climate may help. Avoidance of exposure of the feet to warmth as in riding in

the front seat of an automobile, may alleviate some of the distress, as may also the use of light socks or stockings and of sandals or perforated shoes.^f

When simple measures fail, it may be necessary to anesthetize the skin of the feet by section, crushing, or by the injection of alcohol into such peripheral nerves as the posterior tibial, peroneal and sural. A logical method is to attempt to *desensitize the skin to warmth*. At first, the extremities should be immersed in water at 30° C (86° F.) for 15 minutes twice daily for two or three days. The temperature of the water should then be increased one or two degrees for another period of two days, and this program should be continued. If distress occurs when the temperature of the water is that which ordinarily provokes distress, the treatment should be begun again. If this plan of treatment is successful, the water at the temperature which provoked distress before the treatment was begun will not cause distress. As yet we have no evidence that this plan of treatment is helpful. Histaminase, or "desensitization" with histamine may be tried. The latter should be given subcutaneously twice daily, beginning with 0.05 mg. and increasing each injection by about 0.01 mg., until about 0.15 mg. have been given or until severe reactions occur. Injections should be given for about ten days.

TABLE I
TEMPERATURE STUDIES

Time P. M.	Temperatures in degrees C								Room Temp degrees C
	Left foot				Right foot				
	First Toe	Third Toe	Fifth Toe	Ball of Foot	First Toe	Third Toe	Fifth Toe	Ball of Foot	
2.05	30.4	31.2	30.1	33.8	28.2	29.2	30.5	30.9	24.7
2.25	30.5	31.4	30.7	33.7	27.1	28.9	29.7	30.4	24.3
2.27	31.2*	31.9	31.1	34.1*	27.1	29.0	30.1	30.4	24.1
2.35	32.4*	34.0*	31.9*	34.8*	27.7	29.8	30.7	30.3	23.7
2.41	32.6*	34.6*	33.2*	35.1*	29.3	30.3	31.2	30.5	24.6
2.55	32.3*	34.2*	32.2	35.4*	30.3	29.8	31.0	30.8	23.9

^f Treatment of the painful areas with roentgen rays or radium may help. Such treatment should, of course, be carried out only by an expert.

* The designation (*) indicates the presence of distress.

TABLE II
TEMPERATURE STUDIES

Time 1 M	Temperatures in degrees C						Room Temp degrees C	Con-ent
	Left foot			Right foot				
	First Toe	Third Toe	Ball of Foot	First Toe	Third Toe	Ball of Foot		
9 30	23.8	23.2	24.6	23.4	23.1	24.3	23.4	Patient recumbent
9 40	23.8	23.1	24.6	23.3	23.1	24.2	24.3	Patient recumbent
9 42	23.8	23.2	24.6	23.3	23.1	24.2	24.1	Patient sitting feet wrapped in blanket
10 30	25.4	24.2	25.6	23.4	23.4	24.3	24.0	Patient sitting feet wrapped in blanket
10 47	29.4	26.3	27.5	23.9	23.4	24.4	24.4	Heat applied to blanket
11 15	32.7	32.0	32.2	24.2	23.5	24.7	24.0	Heat in blanket
11 35	36.9	33.0	34.5	31.5	27.5	28.8	24.2	Heat in blanket
11 45	38.1	33.9	35.0	35.4	35.5	30.3	24.0	Heat removed
11 50	36.0	33.2	34.9	35.0	29.0	30.6	23.9	Heat removed
12 00	35.1	34.0	34.8	32.8	28.8	30.7	24.0	Heat removed

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CHAPTER LIV

LYMPHEDEMA OF THE EXTREMITIES

By EDGAR V. ALLEN, M.D.

Etiology Lymphedema which affects human beings appears to have a multiple etiology. The mechanism of its production which is however apparently the same in all cases is predicated on clinical and experimental observations.^{1 2 3} Lymph stasis occurs primarily as a result of obstruction that is produced by inflammatory or noninflammatory processes or by lymphangiectasis which occurs in association with congenital lymphedema. When obstruction occurs the intralymphatic pressure increases and causes dilation of lymph vessels with subsequent insufficiency of the valves forcing lymph to seek new channels which are supplied inadequately with valves. Since valves are very important in causing the lymph to move centrally incompetence of the valves causes further stasis of lymph. The protein content of the lymph increases and fibroblasts proliferate rapidly since the lymph is an excellent culture medium for the growth of fibroblasts. This fibrosis contributes further to lymph stasis. As a result of the increased quantity of lymph in the tissues attacks of acute inflammation may recur producing thrombosis of lymph vessels more stasis of lymph and hence more fibrosis. The cycle which is a vicious one consists of stasis of lymph fibrosis inflammation with further stasis and hence more fibrosis.

CLASSIFICATION OF 300 CASES OF LYMPHEDEMA		CASES
A Noninflammatory		
I Primary		
Precox		93
Congenital		
1 Simple		12
2 Familial (Milroy's disease)		0
II Secondary		
Malignant occlusion		32
Surgical removal of lymph nodes		61
Pressure		1
Roentgen and radium therapy		3

B Inflammatory

I Primary (single or recurrent acute and chronic)	41
II Secondary (single or recurrent acute and chronic)	
Venous stasis	13
Trichophytosis	5
Systemic diseases	5
Local tissue injury or inflammation	33
Filariasis	1

NONINFLAMMATORY LYMPHEDEMA

Primary Lymphedema* Lymphedema precox is an original term applied to a definite clinical syndrome manifested in 93 cases in the group of 300 cases studied. It affected female patients predominantly (87 per cent of the cases), and in the majority of instances (65 per cent) had its onset between the ages of 10 and 24 years inclusively. The term precox is used to denote an early development in many of the cases in this group the onset of symptoms occurred at puberty and the incidence of onset in adolescence was impressive.

The swelling occurs spontaneously and without known cause at the onset the patient ordinarily notices a puffiness about the foot or ankle. The edema is worse during long periods of activity during the menses and in warm weather. Rest in bed and elevation of the extremity produce temporary disappearance of the edema that may affect one lower extremity exclusively (70 per cent in this series) or both legs simultaneously; one extremity may swell months or years after the opposite member has become involved.

The edema ordinarily progresses up the leg slowly and eventually the entire limb becomes edematous over a period of months or years. The spread of the edema may, however, be much more rapid; the entire limb may be involved within a few days or weeks. In many instances swelling is limited to the foot and ankle or does not extend above the knee. Frequently this particular state is doubtless merely a phase of a progressive condition but in other instances it seems to represent the maximal degree of extension of the edema.

Gradually the swelling whatever its limitations becomes more marked; elevation and rest in bed cause its reduction but not its disappearance. The smooth skin becomes roughened and the hitherto soft

* This designation includes no inflammatory type of lymphedema.

edema becomes resistant to pressure. In addition to enlargement of the limb due to edema, there is actual hypertrophy of tissue, and the limb becomes unsightly, ungainly, and uncomfortable. A dull, heavy sensation is present, but there is no actual pain.

The entire course of the swelling is ordinarily one of smooth progression, acute lymphangitis and cellulitis occur infrequently (in 15 per cent of the cases studied). Ulceration of the skin does not occur. The entire history is ordinarily that of conversion of a normal limb into a swollen one; nothing else is noteworthy.

The cause of lymphedema precoc is obscure. The predominant incidence among female patients, the onset in the majority of cases during adolescence, and the accentuation during menstruation tend to indicate that the reproductive organs play a part in the condition. Possibly the additional load thrown on the lymph vessels by rapidly developing reproductive structures induces a functional incompetence of the lymph vessels or allows entrance of infection into the lymph trunks and nodes in the pelvis. Even minor degrees of functional inadequacy, through obstruction in the pelvis, might lead to dilatation of the lymph vessels below, with incompetence of the valves, particularly among women, whose subcutaneous tissues offer little support. The resulting interference with the free passage of tissue fluid into the lymph vessels provides adequate encouragement for the growth of fibroblasts and further obstruction by connective tissue. Homans, Drinker, and Field reported a case in which the lymphedema apparently was of the precoc type. At exploration, greatly enlarged lymph vessels were found in the pelvis; this was an indication of obstruction proximally. It is possible that the entire explanation rests on a congenital underdevelopment of lymph vessels, or their inability to develop quickly enough to supply adequately tissues that are growing rapidly. Limitation of the disease to the lower extremities is striking, and it indicates that gravity is an important factor in the development.

ILLUSTRATIVE CASE: A Jewess, 32 years old, was admitted to the clinic May 15, 1936, complaining of a swollen right extremity. This swelling, which had appeared one year previously in the region of the ankle, had gradually progressed until the entire extremity from the dorsum of the foot to the inguinal region had become involved. During the first few months the swelling had fluctuated in degree, but in the six months pre-

ceding admission it had remained relatively stationary although elevation of the leg for any prolonged period had reduced the size somewhat. There was no associated pain and no history of any preceding trauma or infection.

On examination at the clinic the right leg was found to be about half again as large as the left pitting edema of the dorsum of the right foot right leg and right thigh being present. There was no evidence of disease of the kidneys heart or pelvic structures. Fissures were present between the toes but trichophytes could not be demonstrated microscopically. A Kondoleon type of operation was advised but the patient refused. Adequate supportive bandaging was therefore recommended after elevation of the limb until there had been maximum reduction in the size of the limb.

Congenital Lymphedema This may be either simple or familial. In both types lymphedematous swelling usually of one lower extremity is present at birth. There may be actual hypertrophy of the limb which is the result of fibrous hypertrophy. In other instances the skin is soft and the edema is less resistant to pressure. The two forms do not vary except that in the simple type blood relatives are not similarly affected. In the familial type several persons in the same family have lymph edematous swellings of one or more extremities. The familial type known as Milroy's disease was first described by him as a clinical entity in 1890.

Secondary Lymphedema This may be the result of malignant occlusion of lymph vessels by metastasis of malignant disease of the breast uterine cervix uterus vulva prostate gland bladder testes skin or bones to adjacent lymph nodes. *Such a possibility serves to emphasize the necessity of close scrutiny for evidence of malignant disease in all cases of lymphedema* since swelling may be the first outward manifestation. Pressure outside the lymphatic trunks perhaps occasionally but rarely produces lymphedema. The one case of lymphedema apparently due to pressure in this series seemed to follow the use of a truss for inguinal hernia. Secondary noninflammatory lymphedema may occur in cases of Hodgkin's disease or lymphosarcoma or it may be associated with multiple hemorrhagic sarcoma which has been described by Kaposi or it may follow surgical removal of lymph nodes and lymph vessels for malignant disease distally situated or for tuberculosis or metastasis of malignant disease. The last named condition is the elephantiasis chirurgica of Halsted. Such a condition is not uncommonly seen following radical

* The swelling at o indicates non-inflammatory type of lymph edema.

amputation of the breast and the removal of the axillary lymph nodes for carcinoma. The lymphedema may occur with or without intercurrent attacks of lymphangitis and cellulitis. The irregular interval at which lymphedema occurs after radical amputation of the breast is remarkable. Usually, the arm begins to swell on resumption of activity, but weeks, months, or even years may pass before the extremity becomes edematous. In one instance, the arm was free from swelling for $9\frac{1}{2}$ years, there was no evidence of the recurrence of malignancy to account for the edema, and cellulitis and lymphangitis had not occurred. In such instances, it is possible that fibrosis may be induced by repeated irradiation, thus producing lymphatic obstruction, or, that occult lymphedema, which has been present for years, has resulted in overgrowth of connective tissue and obvious edema. Lymphedema may occur after treatment with radium and roentgen rays. Whether such a result is brought about by the fibrosis caused by irradiation or by metastasis of the malignant disease for which radiation is given cannot be determined with certainty.

INFLAMMATORY LYMPHEDEMA

General Characteristics: The advanced stage of inflammatory lymphedema has been called "elephantiasis nostras streptogenes." All examples of inflammatory lymphedema, exclusive of the chronic form, have one feature in common, single or recurrent attacks of acute cellulitis and lymphangitis. The contrast between lymphedema of inflammatory origin and of the precox type is striking, in the former, progression is by a series of attacks which are impressive in the suddenness of onset, and striking in the severity of systemic reaction; in the latter, the history is one of slowly progressive edema. The usual victim of an attack of cellulitis and lymphangitis of an advanced grade is suddenly seized with a severe chill unpreceded by other symptoms, or, following a short period of distress in the extremity or in its proximal lymph nodes, his teeth chatter, the bed shakes, and he becomes nauseated and vomits. His temperature is between 38.3° and 41.1° C. (101° and 106° F.); in a short time a small, reddened area spreads until a considerable portion of the extremity is swollen, red, hot and tender. The proximal lymph nodes are tender and swollen. The chills recur during a period of 30 minutes to an hour. The high fever persists for a period ranging from a few hours to two or three days, and is accompanied by marked malaise that may persist after

the temperature returns to normal. The abnormal condition of the extremity recedes slowly over a period of from 4 to 14 days, but, after all clinical signs of acute inflammation have disappeared, swelling is present in a greater degree than before the attack. The organism chiefly responsible for the attacks of acute inflammation is the streptococcus. Single attacks leave minor degrees of lymphedema, but successive attacks, which tend to occur progressively more frequently produce increasing edema; each attack is a step toward the final stage, namely, marked lymphedema.

The chronic form of lymphangitis of the spontaneous inflammatory type is exceedingly rare. In such instances, the leg is persistently warmer than its companion member, and a reddish discoloration of the skin exists. In many instances, lymphedema following injury or infection develops without the intervention of acute attacks of lymphangitis and cellulitis or of clinical manifestations of chronic lymphangitis. The infection in such instances is considered to be subclinical. It should be emphasized that lymphangitis, whatever its nature, produces occlusion of lymph vessels by thrombosis which produces lymph stasis which in turn provokes further fibrosis and more stasis of lymph.

Primary Lymphedema*: This term signifies a condition resulting from single or recurring acute attacks or from chronic lymphangitis and cellulitis not secondary to any known local abnormality, such as venous or lymphatic stasis or extraneous infection. In many such instances the lymphangitis appears to occur in much the same spontaneous manner as tonsillitis or phlebitis. In other instances it may be due to infections introduced into the lymph vessels through minor portals of entry unnoticed by the patient. The acute attacks of lymphangitis and cellulitis have been described; each attack leaves a residue of increased edema. In the chronic form of lymphangitis the edema is slowly progressive.

Secondary Lymphedema*: This term indicates a condition resulting from lymphangitis secondary to known causes. The lymphangitis may occur in single or recurrent attacks or in a chronic form. Chronic edema of venous origin may predispose to recurrent attacks of acute cellulitis and lymphangitis, and thus to progressive lymphedema, but such

* This designation indicates inflammatory type of lymphedema.

culty arises Lymphedema can be distinguished without difficulty from the edema of general systemic diseases, such as myxedema, myocardial failure, nephrosis, nephritis or deficient proteinemia, when it is unilateral when it is bilateral, a thorough examination is necessary to exclude these diseases Sarcomas, lipomas and neoplasms of the bone are almost uniformly unilateral, and they produce regional or localized swellings, whereas the edema of lymphatic obstruction is more uniform and extensive When swelling of an extremity is localized, careful roentgenologic studies are invaluable from a diagnostic standpoint Angioneurotic and cyclic edemas are characterized by this intermittence, whereas lymph edema is more constant and disappears during the early phase only on elevation of the limb, well advanced lymphedema responds to this procedure incompletely Enlargement of a limb in arteriovenous fistula is associated with dilatation of and increased pressure in the regional veins analysis of the blood from these veins reveals an oxygen content approaching that of arterial blood If the arteriovenous fistula is congenital, or was acquired before longitudinal growth of the bones ceased spontaneously, the limb is increased in length as well as in circumference All these signs of arteriovenous fistula, except the increased circumference of the limb, are absent in lymphedema

The edema of limbs occasionally noted in lymphosarcoma is probably of lymphatic origin, but recognition of the basic condition is important Ordinarily, in cases of lymphosarcoma, there are enlarged nodes in the regions in which nodes are usually palpable, and in the mediastinum Microscopic examination of a node removed surgically is invaluable when doubt exists It may be remarked parenthetically that it is always important to examine patients with lymphedema carefully for evidence of malignancy Lipodystrophy, characterized by 'fat legs,' is to be distinguished from lymphedema Young women and girls with lipodystrophy are subject to worry, anxiety and even to embarrassment at the supposed cosmetic disfiguration Such reactions have arisen largely as a result of short dresses and hosiery advertisements for aside from a slight disturbance in the symmetry of the body, no disfiguration exists The condition however, is as important as it appears to the patients The characteristic symptoms which lymphedema and lipodystrophy may have in common are predilection for women, similarity in appearance, painlessness and additional swelling of the feet or ankles when patients are on their feet

much, particularly in warm weather. Lipodystrophy is uniformly bilateral and is usually associated with generalized obesity or obesity about the pelvis. The degree but not the extent of lipodystrophy may progress after it is first noted. In contrast lymphedema is usually unilateral, not ordinarily associated with obesity and usually progresses from the foot proximally, except when it is congenital. Attacks of lymphangitis and cellulitis may occur in lymphedema but not in lipodystrophy. Pitting on pressure may occur in both conditions but it is less evident in lipodystrophy. The diminution in size which may follow elevation of the extremities in both conditions is more marked in lymphedema.

The edema of deep thrombophlebitis is usually to be distinguished from lymphedema because the former is similar to lymphedema in so many respects. Well advanced stages of either condition offer little difficulty in diagnosis. The hypertrophied limb with the thickened skin and firm consistency characteristic of lymphedema has little similarity to the limb in cases of deep thrombophlebitis for the latter is marked by softer edema, stasis ulcers, dermatitis and superficial varices. To be sure when attacks of recurrent lymphangitis or cellulitis occur the leg that was originally edematous from venous obstruction acquires an additional element of lymphedema and lymphedema may occur around varicose ulcers as a result of chronic infection. So far as I am aware however pure uncomplicated lymphedema whatever its origin does not lead to ulceration.

It is in the earlier phases of the two diseases that difficulty is encountered. The usual similarity of symptoms includes unilaterality, pitting on pressure, normal skin texture and disappearance of edema following elevation of the limb. Dissimilarities exist in the circumstances of origin, speed of onset and progress, distress experienced by the patient and condition of the superficial veins. Thrombophlebitis with edema usually occurs in the course of or following an illness such as pneumonia or typhoid fever or follows childbirth or operation. During the acute stage a dull aching distress occurs in the area of the involved vein which is tender to pressure, the edema develops rapidly to its fullest extent in the course of hours and the superficial veins are dilated. Lymphedema does not ordinarily occur during systemic disease. The absence of distress is striking except when acute cellulitis and lymphangitis occur, the edema ordi-

narily develops to its fullest extent slowly over a period of weeks months or years and the superficial veins are not dilated

Among dissimilarities the localized distress that occurs in thrombophlebitis is most important Occasionally the two conditions may coexist as in the case of the thrombophlebitic limb that is involved in recurrent attacks of lymphangitis and cellulitis In rare instances it may be difficult if not impossible to distinguish between the two conditions although roentgenologic studies may be of some value The difficulty is particularly great when patients can relate only vague details about the development of the edema

MEDICAL TREATMENT

Medical treatment in order to be of value must be carried out early There is no medical treatment of value when the limb is greatly hypertrophied from the overgrowth of connective tissue Treatment must be instituted when the edema first becomes evident The longer uncontrolled lymphedema exists the more fibrosis occurs and the less efficient medical treatment becomes This point needs to be emphasized for most patients seen at The Mayo Clinic who have lymphedema have had it for a long time and marked fibrosis which cannot be influenced by medical treatment has already occurred

Control of Edema The rationale of attempting to control edema is based on a conception of the condition within the tissues Large lymphatic spaces exist valves are absent or are functionless as a result of dilation of the lymph vessels and lymph which ordinarily moves proximally as a result of muscular activity and the action of valves is static or flows to dependent parts A close parallelism exists with the condition present in varicose veins The problem is one of causing the lymph to move toward the body by preventing stasis We know of no way to accomplish this medically other than by compressing the limb by adequate bandaging

An important first step is elevation of the extremity until as much as possible of the lymph has been removed from the extremity Cloth bandages are of little or no value the support which they give is of little value Elastic stockings are unsatisfactory in many instances for the same reason they tend to stretch and lose their elasticity Adhesive bandages are somewhat more efficient than the previously mentioned supports

The entire criteria for establishing the value of any type of support is control of edema a support which does not prevent swelling when the patient is active is valueless one which prevents swelling is adequate I prefer a pure rubber roller bandage 3 inches wide and 15 feet long Of the three weights available the proper one prescribed for any specific patient depends on the difficulty in controlling the edema Ordinarily the bandage is applied over a lisle stocking beginning by making two turns about the foot two figure of eight turns about the ankle and progressing up the extremity to the knee The toes and part of the heel are left exposed The bandage should be removed and applied in the same manner each time as it becomes shaped to the extremity on repeated use If it is applied too tightly the toes become discolored cold and numb If it is applied too loosely edema results Patients soon become adept at bandaging their legs efficiently The bandage should be removed at mid day and reapplied over a dry stocking after the patient has rested for an hour

The same procedure is repeated at night if the patient is active If he remains home he may remove the bandage and elevate the leg while sitting Patients object to wearing the bandages because of the inconvenience in applying them repeatedly the slight discomfort and then unsightly appearance This is particularly true of women who object to the appearance of the bandaged limb Frequently a well fitting elastic stocking may be used for dress occasions and the use of the heavier rubber bandage may be reserved for ordinary activity It is well to point out to women that the lymphoedematous leg has an abnormal appearance which the bandage increases but little and to emphasize that uncontrolled edema almost invariably causes a gradual increase in the size of the limb I have no information regarding how long the bandage should be worn in some instances it must be used indefinitely in others improvement in circulation of the lymph may occur Once every month or so the bandage can be left off for a day as a trial If edema reappears the support must be worn again

Treatment and Prevention of Inflammation The attacks of acute lymphangitis ordinarily subside spontaneously but recovery appears to be hastened by elevation of the limb and by the application of hot moist packs When reactions are severe streptococcus antitoxins such as those which are used in the treatment of erysipelas or scarlet fever or poly-

valent serums may be used. Blood serum from patients who recently have recovered from an attack of acute lymphangitis and cellulitis may be of value. I have never observed patients to whom I thought it necessary to give antitoxins or convalescent serum for an episode of acute inflammation. Sulfanilamide may hasten recovery.

Almost the entire problem as far as infection is concerned is the prevention of attacks. Unfortunately, we have no proved way of accomplishing this. I have felt that some commercial preparations such as streptobacterin when administered for a long period have been helpful but I can offer no direct evidence. More logical would be the manufacture of an autogenous vaccine from organisms which have been isolated from the tissues at the beginning of the attacks. Again we have no definite evidence that organisms can be isolated regularly during attacks or that a vaccine would be effective in preventing them. I hope that studies with animals which have lymphedema will demonstrate the value of this method. The periodic injection of a therapeutic amount of streptococcus antiserum every few weeks may be of value. Care should be taken to avoid serum reactions. Sulfanilamide may be used intermittently if attacks occur frequently. Portals of entry such as are present between the toes in the presence of trichophytosis should be removed. When attacks of acute inflammation recur trichophytosis should always be suspected and vigorously treated if present.

SURGICAL TREATMENT

The necessity of surgical treatment of lymphedema is a frank admission of failure of medical treatment in those instances in which the best medical treatment has been carried out. In many instances however surgical treatment is necessary because medical treatment has been carried out inefficiently or not at all. Selection of cases of lymphedema for surgical treatment depends on the etiology and severity of the lesion. There is no need to perform the operation in cases in which malignancy exists or in cases in which causative conditions of greater importance than lymphedema such as Hodgkin's disease or pelvic tumors are present. Unfortunately we cannot promise the patient who has mild lymphedema a great deal of benefit. The leg can be restored to normal size and to nearly normal shape but there is no assurance that such restoration will be in any way permanent unless an adequate type of supporting bandage is worn for an indefinite period. Therefore the more severe the case the

more one can offer in the way of relief with surgical treatment. The history of attacks of cellulitis is not a contraindication to surgical treatment, but on the other hand, one can reasonably assure patients who have had recurrent attacks of cellulitis that the frequency of these attacks will be reduced. One should, of course, not operate during an attack of cellulitis.

The immediate preoperative care of the patient should consist of rest in bed for a few days, with the affected limb elevated continuously to reduce the edema. A sling, which supports the limb at an angle of at least 45° , should be used. Diuretics, such as salyrgan, and firm bandaging may hasten the disappearance of edema. In three to six days, as a rule, the amount of lymph in the limb will be minimal which will make the surgical procedure much easier than it would have been before. The various surgical methods which have been used for the treatment of lymphedema have been reviewed by Ghormley and Overton. The procedure used at the clinic is that which was described originally by Kondoleon and modified by Sistrunk.

The actual operation should be carried out under spinal anesthesia, using a tourniquet, applied as high as possible on the affected limb and usually without the customary towel beneath it. Two incisions are made along one side of the thigh or arm, extending as high as the lymphedema, so that a long strip of skin may be excised in an elliptical manner. The amount of tissue that can be removed will depend on the width of the strip of skin between the two incisions. As much as possible should be removed in order to reduce the size of the extremity greatly.

When the incisions have been made through the skin the margins of skin to be left are undermined for a distance on either side, approximately half of the circumference of the extremity. The skin, subcutaneous tissue, and as much as possible of fascia, except that at the intermuscular septa and at joint capsules, are removed in one piece. Care should be taken not to damage the main cutaneous nerves. After removal of the tissue, the wound should be closed with interrupted sutures. No attempt is made to secure hemostasis, only the larger branches of the veins being ligated.

In closing the wound, one should not hesitate to apply as much tension as is necessary; considerable tension may be applied without fear of sloughing. Indeed, it is better to have some tension than to have an excess of skin remaining redundant. A pressure bandage is applied and

the tourniquet released slowly, taking several minutes to allow the circulation actually to return to normal. We believe this step to be of considerable importance as it is possible that the sudden flooding of the circulation with material from the large wound may have had something to do with the high incidence of surgical shock. The limbs are not elevated after the operation, so that materials from the wound get into the general circulation somewhat more slowly than if the limbs were elevated. Apparently, as a result of the methods mentioned, the incidence of post-operative shock in these cases has been reduced to almost zero.

After ten days the dressing is changed, and if healing has advanced sufficiently, the patient is allowed to be up. Adequate bandaging, such as that described with the medical treatment, is necessary for an indefinite period. Crutches or cane are unnecessary when the patient resumes walking.

It is customary to wait from three to six months between operations. That is to say, we treat one side of an extremity and allow healing to become complete before operating on the other side. Occasionally patients get enough improvement from the operation on one side to justify omitting the second stage, but, as a rule, a much better result will be obtained if both sides are subjected to operative treatment.

Ghormley and Overton recently have reviewed the results in 64 cases of lymphedema, in which the condition was treated surgically in the past ten years. In 41 of these cases there was improvement of varying degrees; no improvement was noted in eight cases, in six cases the patients had died and in nine cases the patients had not been traced.

Recurrent infection such as cellulitis and lymphangitis, which had been present in 25 instances preoperatively, was worse after operation than it had been before, in six cases; was improved in nine cases, and had disappeared in 11 instances, as a result of the operation.

There is considerable doubt that the benefit, which follows, results from that effect which Kondoleon originally intended; namely, anastomosis of the superficial and the deep lymphatics, if, indeed, this actually occurs. Since the obstruction in many instances appears to be in the lymphatic vessels within the pelvis, little or no benefit would follow the shunting of lymph flow into the deep vessels in the leg, as these are continuous with the obstructed lymph vessels. The operation appears to me to be predominantly a plastic procedure, removing large valveless lymph spaces

and hypertrophied connective tissue. As such it is not a physiologic procedure but simply a plastic one which corrects deformity. Since lymphedema has been produced experimentally it is to be hoped that better methods of surgical treatment will be discovered. Perhaps the most satisfactory procedure will be found to be a combination of the plastic operation of Kondoleon and one designed to carry the lymph around the area of obstruction such as anastomosis of the lymphatic vessels of the extremity with those of the trunk. Such a procedure as the latter has been described by Gillies and Fraser.

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CHAPTER LV

SUDDEN EMBOLISM AND THROMBOSIS OF ARTERIES OF THE EXTREMITIES

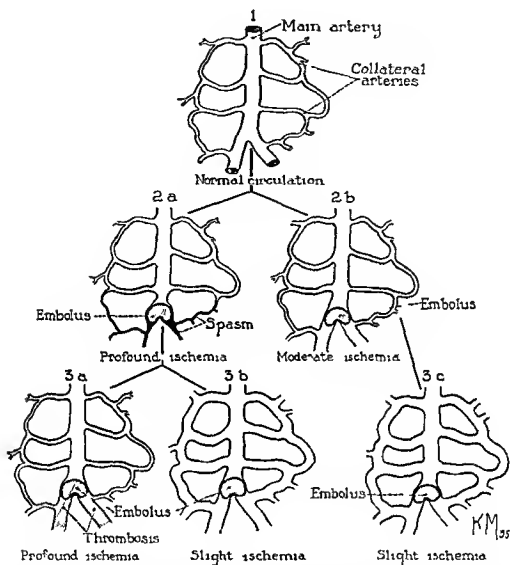
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ETIOLOGY

The arteries of the extremities may be occluded suddenly as a result of embolism or thrombosis (Table I). The heart is the chief source of emboli. Disease of the aortic or mitral valves and thrombosis on the walls of the heart due to any cause may give rise to the detachment of thrombi and their transportation by the blood to the peripheral arteries which suddenly become occluded. An embolus of cardiac origin is more likely to develop when irregularities of rhythm such as auricular fibrillation or flutter exist than when the rhythm is normal. A presentation of the various types of heart disease which may lead to embolism is beyond the scope of this paper. The subject has been reviewed adequately by Williams^{23, 24}. It is hardly necessary to mention the transportation of a clot from the veins through a patent foramen ovale as this must occur rarely.

A thrombus on the walls of the arteries of the greater circulation may give rise to embolism distally. Such thrombi may occur in aneurysms on arteriosclerotic plaques as a result of injury and inflammation. The sclerotic aorta is a common source of an embolus. At necropsy one may observe numerous examples of projection of plaques into the lumen and thrombi around these projections are not uncommonly observed. In specific instances in which no other disease of the heart or large arteries can be demonstrated the emboli probably originate from thrombi on the walls of the arteries.

Local thrombosis may occur suddenly in the arteries themselves owing to a number of causes. Symptoms of sudden arterial occlusion occur in about ten per cent of cases of thromboangitis obliterans. Just why the symptoms of this final event are acute in some cases and of gradual onset (1632)



The probable course of events in arterial embolism. 1 Normal arterial circulation at a specific point is maintained by the main and collateral arteries. 2 a The embolus may be fixed at the point of lodgment by spasm which likewise affects the collateral arteries producing profound ischemia as both arterial pathways are occluded. 2 b If spasm does not occur only moderate ischemia results since the collateral arteries continue to function. 3 a If arterial spasm persists for a considerable period widespread arterial thrombosis results when the spasm disappears since the intima has been greatly damaged by prolonged ischemia. Under these circumstances there is profound diminution in the blood supply to the extremity. 3 b If arterial spasm is relieved promptly and the function of the collateral arteries is increased the resulting ischemia is only slight in spite of the fact that the main pathway is occluded. 3 c When arterial embolism does not result in spasm the circulation can be greatly improved by increasing the function of the collateral arteries only slight ischemia results.

in others cannot be stated. The different results seem to represent variations in the speed of the process, in the size of the artery involved, and in the extension of the thrombus. In periarteritis nodosa, thrombosis occurs, but usually the process is one of days rather than hours. However, it seems advisable to include this disease in my classification. Mycotic arteritis, or the effect of bacterial toxins on the walls of arteries, appears

TABLE I

THE ETIOLOGICAL CLASSIFICATION OF SUDDEN ARTERIAL OCCLUSION (ALLAN)

Embolism	Cardiac	Mitral and aortic valvulitis;
		Bacterial:
	Venous	Acute
		Subacute
	Arterial	Mural thrombosis
		Failing heart from any cause
		Through patent foramen ovale
Thrombosis	Inflammatory	Mural thrombosis;
		Aneurysm
	Degenerative	Arteriosclerosis
		Trauma
	Traumatic	Inflammation
		Thromboangiitis obliterans
	Hematogenic	Periarteritis nodosa
Ligation and severance		Mycotic arteritis (severe infections)
Miscellaneous		Arteriosclerosis
		Surgical
		Cervical rib
		External trauma
		Gunshot and stab wounds
		Thrombophilia
		Septicemia, peritonitis, pneumonia, etc.

to account for sudden occlusion occurring in severe infections such as septicemia, pneumonia, peritonitis, and more rarely in such conditions as tuberculosis and influenza. There may be an additional factor of increased coagulability of the blood; hence, this type of sudden arterial occlusion is classified likewise under thrombosis of hematogenic origin. In generalized infections, such as septicemia, the original lesion is, apparently, inflammation of the arteries which leads to thrombosis. Arteriosclerosis of the arteries of the greater circulation causes thrombosis by

roughening of the intima or projection of atheromatous plaques into the lumen of the artery. As in *thromboangitis obliterans* the final stage of occlusion is always thrombosis and similarly evidence is not at hand to explain why the symptoms are of sudden onset in some cases and gradual in others. Only about ten per cent of cases of arteriosclerosis obliterans are characterized by sudden occlusion. Thrombosis may likewise occur as a result of external trauma such as that which occurs as a result of large cervical ribs, gunshot and stab wounds and as a sequel to severe injury to an extremity or unusual effort. The latter factor may produce thrombosis by causing projection of a calcareous plaque into the arterial lumen.

One of the most interesting causes of sudden arterial occlusion is increased coagulability of the blood or thrombophilia, a syndrome which has been described by Nygaard and Brown who reported five cases. According to these authors the characteristics of this condition are sudden occlusion of large arteries and veins of apparently normal subjects, absence of the usual clinical features that characterize the chronic occlusive arterial diseases and embolism, minimal pathologic changes in the involved vessels, changes in coagulation of the blood occurring during episodes of thrombosis and multiple areas of thrombosis which are not ordinarily observed in other diseases characterized by thrombosis.

Sudden occlusion of arteries of the extremities may occur following operations during which the main arteries are not apparently injured. Perhaps it results from extension of thrombi into the main arteries from smaller branches. This is not always a possibility, however, as is evidenced by a case of sudden occlusion of the arteries of the left arm following resection of the stomach for carcinoma. In this specific case in which the patient was a woman 65 years old it was assumed that the slowed blood stream subsequent to partial immobilization of the extremity following operation led to the deposition of a thrombus on a sclerotic mural plaque. Naturally, causes effective at any time may cause sudden occlusion following operation. Malignant cells may invade arteries and may possibly cause occlusion of the arteries of the extremities. I can offer no direct evidence of this although the process has been described in the pulmonary arteries by Greenspan. In two of the cases mentioned in this report there was an associated extensive malignant involvement of the pelvic structures. These instances of sudden occlusion of arteries of uncertain origin are included under the term miscellaneous.

The determination of the exact cause of sudden arterial occlusion is not always easy. When disease of the heart is present, and particularly if it is associated with disturbances in rhythm, sudden occlusion of the arteries can usually be attributed to an embolus from the heart. When it occurs in the presence of characteristic evidence of thromboangitis obliterans or arteriosclerosis obliterans such as antecedent symptoms of these diseases and evidence of slow occlusion of arteries in other extremi-

TABLE II
THE CAUSES OF 100 CASES OF SUDDEN ARTERIAL OCCLUSION

	Embolism*	Thrombosis*
Heart disease	41	
Pelvic carcinoma	2	
Patent foramen ovale	1	
Arteriosclerosis	1	32**
Operation for cervical rib	1	0
Thromboangitis obliterans		4
Following operations		8†
Ligation		1
Infection		5‡
Cervical rib		1
Indeterminate		3

* Not always absolute diagnosis

** Diabetes in five cases. Twenty patients had symptoms previously of arteriosclerosis obliterans. Disease of the coronary arteries with or without decompensation or arrhythmia present in 21 cases. Arterial occlusion in some instances was probably due to embolism but the diagnosis of thrombosis was made in all cases.

† Carcinoma of cervix in one case, hysterectomy in 11; division of posterior root of fifth cranial nerve in one; carcinoma of colon in one; amputation of cervix in one; herniotomy in one; resection of stomach for carcinoma in one.

‡ Malaria, influenza, osteomyelitis, one case each; peritonitis in two cases.

ties, and the absence of other obvious causes, sudden arterial occlusion can safely be attributed to thrombosis occurring as a part of the diseases mentioned. It is when no obvious cause exists that difficulty is encountered in explaining the situation. Then the best one can do is to hazard a guess after all available information is considered. Fortunately, the determination of the exact cause is secondary to rational treatment of the diminished blood supply resulting from the occlusion. The various etiologic factors in our cases are summarized in Table II.

SYMPTOMS

It is a common belief among physicians that sudden arterial occlusion is characterized at onset by an abrupt attack of excruciating pain. That

this is true in some cases cannot be denied but my data indicate unequivocally that the symptom mentioned is an inconstant companion of sudden arterial occlusion. I wish to stress parenthetically that it is dogmatic adherence to this old criterion of arterial embolism or thrombosis that contributes to inadequate or inaccurate diagnosis and the poor treatment which invariably follows. The diagnosis of arterial occlusion

TABLE III
THE SYMPTOMS OF SUDDEN ARTERIAL OCCLUSION

Symptoms	Embolism (46 cases)		Thrombosis (24 cases)	
	Symptoms occurred acutely in 24 cases* Subacutely in 22 cases**		Symptoms occurred acutely in 21 cases* Subacutely in 30 cases**	
	Total Cases	First noted Cases	Total Cases	First noted Cases
Pain	33	22†	42	32
Numbness	19	8	22	8
Coldness	14	6	23	3
Tingling	5	0	0	0
Tenderness	3	0	1	0
Cramps	1	1	3	3
Itching	1	1	0	0
Pallor	2	2	11	1
Burning	0	0	3	1
Fullness	0	0	4	0
Unknown‡	6		6	

* Very suddenly

** Developed in one to five hours

† Acutely in 17 cases

‡ Patients in coma or symptoms not noted

is easy when gangrene is obvious and it is then equally futile. *Diagnosis must be made early.* This necessitates a knowledge of the early symptoms of sudden arterial occlusion. For suspicion that it exists must encourage the examination which permits the diagnosis.

In 47 per cent of our cases (Table III) the symptoms appeared suddenly and reached their maximal intensity quickly; in the remaining cases the development of symptoms was gradual, requiring from one hour to several hours to reach a full development. These figures emphasize the fact that the symptoms of sudden arterial occlusion do not always occur abruptly. In only 54 per cent of cases was pain the initial symptom.

On the basis of these data, sudden arterial occlusion would be suspected in only about half of the cases in which it had occurred if abrupt pain was considered the only symptom of importance. Numbness, coldness and tingling may be paramount symptoms, either occurring singly or in varied combinations with pain and with each other. Loss of muscular power, amounting in some instances to total paresis, is rarely noted by the patient. This is due apparently to the natural tendency to immobilize a painful extremity. I do not know definitely the explanation for the varied symptoms noted, but it is probably intimately linked with the suddenness and extent of the organic occlusion and the degree of arterial spasm associated with it.

There is very little of importance in the general symptomatology. When serious organic disease exists, such as valvular heart disease associated with decompensation, for example, symptoms of it dominate the clinical picture. Individuals who are not seriously ill previously manifest varying degrees of tachycardia and anxiety. The body temperature is rarely significantly altered. When severe pain exists the facies are drawn and pallid; perspiration may be profuse.

Interpretation of Symptoms: All but one of the symptoms and findings observed in sudden arterial occlusion are of obvious origin. Pulsations are absent because the artery is occluded proximally. Coldness of the extremity is due to diminished arterial circulation. Diminution or loss of sensory perception and motor power are manifestations of ischemia of nerves and muscles. The pain which supervenes when tissue is in the process of disintegration is similar to that noted in death of tissue from many causes. The symptoms of ischemic neuritis described by Goldsmith and Brown are due to degenerative changes in the nerves resulting from ischemia. The cause of the pain that appears suddenly in a severe form, in many instances as the first manifestation of arterial occlusion, is more difficult to explain. Why is it that slow occlusion of large arteries may occur without pain, a situation well demonstrated by widespread arterial occlusion in thromboangiitis obliterans and arteriosclerosis obliterans, whereas one of the chief symptoms of sudden arterial occlusion is pain? For some time we have felt that ischemia following sudden arterial occlusion was too profound to be caused by the organic occlusion alone.

It seems unreasonable to us that sudden occlusion of the popliteal artery for example should cause gangrene in about half the cases when we frequently see individuals with chronic occlusion of the popliteal arteries without any great degree of impairment of the arterial circulation. There seems to be a factor contributing to the ischemia in addition to simple interruption in the continuity of the lumen of the artery. Always when I have observed patients with sudden arterial occlusion whose pain has begun abruptly I have been dissatisfied with our explanation of the cause of the pain namely ischemia. Recently I have believed that the pain and profound ischemia were caused in a large degree by arterial spasm. This is supported by observations by other investigators. Seifert and others have observed arterial spasm in the involved artery during the operation of embolectomy. After observation of patients with arterial embolism Seifert concluded that the severe pain was due to arterial spasm. In a study of experimentally produced embolism Gosset Bertrand and Patel observed that the embolus was fixed at the point of lodgment by arterial spasm. They observed likewise that the lowered temperature of the extremity in which a main artery had been occluded by an embolus was gradually replaced by normal warmth a few hours afterward indirect evidence that the original diminution in warmth was due to arterial spasm which relaxed in the course of a few hours to allow normal warmth to return to the extremity. Denk was so impressed by the probability that arterial spasm contributed to the diminished arterial circulation that he administered papaverine hydrochloride which is an antispasmodic as part of the treatment of sudden arterial occlusion. The results were good. Herrmann and Reid have shown that alternate suction and pressure applied to an extremity which has sustained sudden occlusion of the main artery result in marked improvement of the circulation. Since the procedure does not influence the occluded area itself it must act by relieving spasm and inducing a greater flow of blood through inadequately dilated collateral arteries.

The best observations on changes in temperature of the extremity following experimental ligation of the external iliac artery are reported by Mulvihill and Harvey. Following the procedure mentioned the temperature of the leg was reduced to the level of that of the room in two to six hours after a reduction of 55 to 16.5° C (10 to 30° F). This temperature persisted for several hours then there was a gradual or rapid

increase, so that in an average of about 13 hours after ligation of the artery the extremity was again as warm as before the operation was performed. If sympathectomy was performed when the temperature of the foot was low, there was an immediate increase in warmth to a temperature level equaling that before ligation occurred. If sympathectomy preceded ligation, no decrease in temperature occurred following the last procedure. These experiments offer unequivocal evidence that the decrease in temperature following ligation is due to a vasomotor mechanism. One cannot say that this vasomotor effect is characterized by active spasm or inadequate vasodilation. This observation is of some importance as active spasm might well be associated with pain, whereas it is difficult to conceive that a passive state of inadequate dilation would be. Herein may be the explanation for varying degrees and types of pain following various types of sudden arterial closure.

Statements concerning the origin of the severe pain following arterial embolism are based to a large extent on logic rather than known facts. If we assume that the lodgment of the embolus and the severe pain occur nearly simultaneously, we know of no other mechanism than arterial spasm which effects profound ischemia to account for the distress. Seifert, who has given this phase of the problem consideration, believed this to be the case and relates two experiences to support his contention: A woman, aged 44 years, was afflicted suddenly with evidence of occlusion of the axillary artery; the pain affected the entire area from the middle of the arm distally. Five hours later the pain suddenly changed, so that it involved only the extremity, from the junction of the middle and upper thirds of the forearm distally. At operation no embolus was found in the axillary artery; amputation was necessary and the embolus was found in the cubital artery. Seifert believed the change in the location of the pain was due to a shift of the embolus to a more distal position. In the case just mentioned and in another, pain disappeared after arteriotomies, although gangrene supervened and amputation was necessary. Seifert believed that the relief of pain was due to the disappearance of spasm. He pointed out that sudden occlusion of an artery alone cannot be responsible for the pain observed in embolism, since ligation was often necessary for war injuries, yet the type of pain which occurs in arterial embolism was usually absent.

The probability that arterial spasm is responsible for the pain in embolism either directly or as a result of the ischemia it produces is so logical and fits so well with recorded observations regarding suddenness of onset, severity, and the difficulty of localizing the pain that we believe there is a distinct cause and effect relationship. Unfortunately, no observations based on direct visualization are available to indicate the extent of the spasm. However, the experimental work of Mulvihill and Harvey indicates a widespread localization below the point of occlusion, since interference with the circulation is so great that the temperature of the part is reduced to that of the room in which the experiments were performed.

The duration of symptoms after sudden arterial occlusion is variable. If marked vasodilation is induced soon after the onset, the symptoms may be relieved promptly and completely, as reported by Herrmann and Reid, Denk, and Allen and MacLean, who used intermittent suction and pressure and papaverine. If these methods are not used, the major symptoms may disappear in from 24 to 72 hours. This cessation of symptoms may indicate eventual recovery or eventual gangrene. When gangrene is definitely established, the symptoms are ordinarily mild. In cases in which sudden arterial occlusion does not lead to gangrene, the symptoms due to sudden occlusion may merge imperceptibly into those of ischemic neuritis, described by Goldsmith and Brown. The pains tend to be paroxysmal and severe and to cover large areas, which do not correspond to any definite nerve distribution. They may persist for weeks or months.

Even when ischemic neuritis does not occur there are ordinarily some evidences of residual impairment of circulation, such as vasomotor changes, coldness, intermittent claudication, hyperesthesia, and so forth.

DIAGNOSIS

The incidence of diagnosis of sudden arterial occlusion parallels roughly the suspicion by the physician that it exists. If one examines the extremities for the condition only when severe pain, pallor, and coldness exist, many cases will be overlooked. As stated in the preceding paragraphs, the symptoms are frequently minimal and bizarre. The habit of examining the arteries of an extremity for pulsations when distress exists is a valuable one, and the procedure should be carried out routinely under the circumstances noted. It is an unfavorable commentary on this

phase of diagnosis that the physical examination often is considered complete although no notation is made of the state of pulsations in the arteries of the extremities. A comparable situation would be failure to examine the heart when the patient complains of dyspnea.

The symptoms indicative of sudden arterial occlusion have been mentioned previously. The chief findings are absence of pulsation in some of the acral arteries in which pulsations were previously present, lowered surface temperature, pallor, and the loss or diminution of reflexes, sensation and muscular strength.

Easily palpable under ordinary circumstances are the brachial, radial, femoral, popliteal, dorsalis pedis and posterior tibial arteries. Some practice is required to feel pulsations in the ulnar arteries of normal subjects. In obese subjects determination of the state of pulsations, particularly those in the brachial, ulnar, popliteal and posterior tibial arteries may be more difficult. In spite of these difficulties the absence of pulsations in arteries which were known or assumed to have been palpable previously is the most important diagnostic sign. Observation of this abnormality in conjunction with lowered surface temperature and pallor of an unusual degree is pathognomonic of arterial occlusion. Additional findings of hyperesthesia, anesthesia or paresis are confirmatory. Thermometers are not needed to determine lowering of the surface temperature which can be estimated with sufficient accuracy by alternately placing the back of the hand on the normal and diseased extremities.

Thrombophlebitis is the only condition which may be differentiated with difficulty from sudden arterial occlusion. Ordinarily the normal temperature, edema, distended veins and normal arterial pulsations observed in cases of thrombophlebitis serve as an adequate contrast to the lowered temperature, collapsed veins and diminished or absent pulsations in the arteries in cases of sudden arterial occlusion. However we have observed that arterial pulsations may be absent temporarily in phlebitis apparently as a result of spasm. Pallin observed such an occurrence during operation for supposed embolism. He observed that the femoral vein was thrombosed and that the femoral artery was occluded by spasm. In sudden arterial occlusion the veins may be distended usually after many hours have elapsed as a result of secondary venous thrombosis. Under such circumstances close attention must be given to the

mode of onset and the known possibilities of embolism. In rare instances the diagnosis may not be clear until many hours have elapsed.

Localization of the embolism is usually not difficult and is of importance only when embolectomy is contemplated, or from a prognostic standpoint. Knowledge that emboli usually lodge at bifurcations, owing to the fact that the emboli will lodge at a point where the caliber of the artery is suddenly reduced, is of importance. Palpation is likewise of primary value in localizing areas of sudden arterial occlusion. The point of sudden arterial occlusion is just distal to the area where normal pulsations are noted. Unfortunately for extreme accuracy the anatomic arrangement of arteries does not allow palpation of them throughout their entire course. Extreme tenderness over the area of occlusion is not uncommon. The line at which the temperature of the skin changes from low to normal is likewise of importance, and it can be determined by passing the back or side of the hand proximally from the distal portion of the extremity. This line is located roughly just above the ankle in occlusion of the popliteal artery, and at the juncture of the lower and middle thirds of the thigh in occlusion at the bifurcation of the femoral artery. When the common iliac artery is occluded, the point is located at about the juncture of the middle and upper thirds of the thigh. Similar relationship of the location of the embolus and the line of sharp change in temperature is observed in the upper extremity. Diminution or loss of motor power and sensation, when it occurs, is ordinarily distal to the line of sharp change in the temperature of the extremity. When arteries are paired, as the radial and ulnar or dorsalis pedis and posterior tibial arteries are, occlusion of one of them may produce only minimal changes in temperature, color, and so forth, as the companion artery continues to carry blood to the distal parts. Our data regarding arteries and extremities involved are summarized in Table IV.

THE COURSE OF EVENTS IN SUDDEN ARTERIAL OCCLUSION

All cases of sudden arterial occlusion have one common factor, interruption of continuity of the arterial lumen. In many instances, particularly when pain occurs suddenly and is severe, it appears that arterial spasm is present. In other instances the collateral arteries fail to dilate adequately enough to allow survival of the limb. When pain is minimal and the diminution of the blood supply is not marked, it appears that spasm is absent and circulation through collateral arteries is adequate.

If the mere occlusion of the artery plays a minimal rôle in the diminution of blood supply, why should not all extremities survive, since the experimental work of Mulvihill and Harvey, and of Gosset, Bertrand, and Patel, indicates that additional diminution of blood supply effected by spasm or inadequate dilatation of collateral arteries is temporary and

TABLE IV
THE ARTERIES AND EXTREMITIES AFFECTED IN 100 CASES
OF SUDDEN ARTERIAL OCCLUSION

Arteries Involved, Cases

	<i>Embolism</i>	<i>Thrombosis</i>
Aorta	1	0
Iliac	2	1
Femoral	18	19
Popliteal	23	21
Posterior tibial	5	3
Anterior tibial	0	1
Dorsalis pedis	0	2
Axillary	0	2
Brachial	8	8
Radial	0	1
Ulnar	1	2
Digital	1	0

Extremities Involved, Cases

<i>Embolism</i>				<i>Thrombosis</i>			
<i>Arm</i>		<i>Leg</i>		<i>Arm</i>		<i>Leg</i>	
<i>Right</i>	<i>Left</i>	<i>Right</i>	<i>Left</i>	<i>Right</i>	<i>Left</i>	<i>Right</i>	<i>Left</i>
6	4	20	27	3	10	23	24

corrected in a few hours? We cannot answer definitely, but we believe that ischemia effected by arterial spasm or inadequate dilatation of collateral arteries, if prolonged, produces changes in the intima of arteries and veins, which in turn produce widespread vascular thrombosis in the extremity when the spasm abates or dilatation of collateral arteries occurs. The diminution of blood flow is brought about, then, by organic changes alone, as the functional element has disappeared. It is true that venous thrombosis is an almost constant accompaniment of sudden arterial occlu-

sion terminating unfavorably. This conception serves to emphasize the need for prompt treatment either medical or surgical when sudden arterial occlusion occurs since delays may lead to extensive thrombosis.

PATHOLOGIC CHANGES FOLLOWING EMBOLISM

An excellent experimental study of this subject has been presented by Gosset, Bertrand and Patel. Animals were killed one, two, three, four, five, six, seven and eight days after embolism was produced experimentally and the arteries at the site of occlusion were studied. Septic emboli contained and were surrounded by bacteria 24 hours after embolic occlusion. The musculature of the artery was affected by hyaline degeneration and severe inflammation was present in the adventitia. The following observations pertain only to occlusion by aseptic emboli. At the end of the first day the internal elastic lamina had lost its undulating character and the musculature had the appearance of aseptic necrosis. At the end of the second day hemorrhagic infiltration into the perivascular fatty tissue was noted in addition. Twenty-four hours later the periphery of the clot was fibrinous in nature and infiltrated with polymorphonuclear leukocytes and pigmented macrophages; the endothelium had disappeared largely and the muscle fibers for the most part had disappeared. Subsequent observations showed chiefly organization and fibrosis. These investigators believed that the changes noted were due in part to interference with nutrition of the artery as a result of its distention by the embolus.

PROGNOSIS

The outcome in cases of sudden arterial occlusion leaves much to be desired. In my series of 57 extremities in which sudden arterial occlusion occurred as a result of embolism gangrene supervened in 26 instances or 45 per cent. In 31 of 60 extremities in which sudden arterial occlusion occurred as a result of thrombosis gangrene supervened an incidence of 50 per cent (Table V). One may say then that gangrene occurred in about half of all cases of sudden arterial occlusion. Admittedly the treatment of these patients was not the best according to my present understanding of the events which occur in sudden arterial occlusion. My only excuse for the poor results is that the treatment was the conventional one at the time the patients were observed. More modern therapy should be productive of a much greater incidence of recovery. Denk's report

of recovery in seven of ten cases* as a result of the use of papaverine and Herrmann and Reid's report of recovery in all of ten cases as a result of treatment with alternating positive and negative pressure, indicate more logical therapy and hold out hope that the figures in our series may be greatly improved in future cases of sudden arterial occlusion.

It is of some interest that in my series the ultimate outcome could be predicted 24 hours after the onset of occlusion in about 80 per cent of cases of embolism and in only about 50 per cent of cases of thrombosis. This is as expected since thrombosis may be progressive and embolism is ordinarily a single concise event. My data do not allow delineation

TABLE V
THE FINAL RESULT IN 100 CASES OF SUDDEN ARTERIAL OCCLUSION

46 cases of embolism involving 57 extremities		54 cases of thrombosis involving 60 extremities	
Gangrene	26*	Gangrene	31*
12 amputations with 5 postoperative deaths		15 amputations with 7 postoperative deaths	
12 deaths without amputation**		14 deaths without amputation**	
Recovery†	31*	Recovery‡	29*
Death without gangrene in three cases		One death with 0 of gangrene	

* Applies to number of extremities involved

** In two cases two extremities involved

† Residual signs of arterial insufficiency in many cases

‡ In one case 10 extremities involved

of many of the factors determining prognosis. Age is important. Of patients more than 60 years of age with embolism gangrene supervened in 73 per cent and of patients more than 60 years of age with thrombosis gangrene occurred in 83 per cent. The respective figures for patients less than 60 years of age were 32 per cent and 42 per cent. This is likewise expected since older patients have less vitality and the ability of collateral circulation to develop is apparently inferior. Moreover atheromatous changes are extensive and encourage progressive thrombosis. It is our impression that when one of two companion arteries† is involved the chances of recovery or of minimal degrees of gangrene are greatly increased. The condition of the patient is important. This is not definitely worthy of emphasis as far as recovery of an extremity is concerned but chiefly because of the possibility of death from other causes such as

* In 10 cases in which the results were bad the occlusion was old and irremediable damage had already been done.

† Examples of companion arteries are the radial and ulnar arteries and the dorsalis pedis and posterior tibial arteries.

is present in cases of cardiac decompensation and because of the possibility of further embolism either to the extremities or more vital structures. It is apparent that the probabilities of survival of the patient are less when he suffers arterial embolism from a decompensated arrhythmic heart than if he sustains thrombosis resulting from arteriosclerosis. Another impression gained from our data is that thrombosis particularly that due to arteriosclerosis produces lesser areas of gangrene than embolism does. It is to be hoped that future studies will allow concise and accurate delineation of the factors important in a prophetic way.

TREATMENT

There can be no reasonable doubt that a great many patients with sudden arterial occlusion are poorly treated. One frequently sees the extremity elevated and surrounded by hot water bottles. Both procedures are ill advised. Elevation diminishes somewhat the flow of blood to the extremity and the direct application of heat may cause burns which contribute to the difficulty. Barker has shown many times that tissue deprived of its normal supply of blood is extremely sensitive to thermal and chemical agents which are well tolerated by normal extremities. *No treatment at all is better than elevating the extremity and surrounding it with hot water bottles.*

It is beyond the scope of this presentation to consider the surgical treatment of arterial embolism namely embolectomy. This phase of the subject has been adequately reviewed by Danzis Allen and Pemberton. The recent papers of Herrmann and Reid, Allen and MacLean and Denk emphasize that embolectomy may soon be considered an unnecessary procedure as excellent results may follow simpler measures. However if circulation has not been markedly restored after three or four hours of intensive medical treatment embolectomy should be considered. The surgeon may produce astonishing results even after medical treatment has failed.

There are three important don'ts in the treatment of sudden arterial occlusion. Don't delay treatment for more than two or three hours, don't elevate the extremity and don't subject it to heat which exceeds by more than a few degrees the temperature of the body. Delayed treatment means a poor prospect of recovery in those instances in which recovery would not occur spontaneously. *Until the custom disappears entirely it*

cannot be emphasized too frequently that tissue deprived of its normal blood supply does not tolerate heat well. Hot water bottles are frequently of a temperature which exceeds 65.6° C (150° F) and will almost invariably provoke burns if allowed to come in contact with the skin. I believe that not uncommonly, recovery would have occurred if burns had not resulted from hot water bottles.

Continuous intravenous infusion of appropriate amounts of heparin should be begun at once^{17, 18}. The time for coagulation of the blood should be kept as nearly as possible at three times normal. This serves to prevent extension of thrombosis and to prevent the thrombosis which may occur after operation if embolectomy is performed. Treatment with heparin should be continued until recovery or until gangrene is inevitable. If successful operation is performed treatment with heparin should be continued for several days.

Opiates should be given immediately to control pain as in myocardial infarction. The ingestion of alcoholic drinks is ordinarily of great benefit in this regard apparently because alcohol is an antispasmodic as shown by Brown and Cook as well as an anodyne. The extremity should be wrapped in cotton which can be held in place with a roller bandage to preserve the natural warmth of the extremity. A cradle open at one end containing not more than one or two bulbs may be placed over the extremity. The temperature of the air about the limb should not exceed 40.5° C (105° F). The extremity should be placed in a dependent position. When the legs are involved the head of the bed should be elevated when the arms are involved the patient should be in the semi sitting position. Vasodilators should be given to relieve arterial spasm if present. Papaverine hydrochloride which is a vasodilator when given intravenously or into the artery proximal to the area of occlusion in amounts of 0.032 Gm (1/2 grain) will produce improvement in the circulation of the limb within a few minutes if it is effective at all. Care should be taken that the solution of papaverine is physiologically active. If the first injection does not cause improvement it is questionable that further trial with this drug will benefit the circulation. Denk who originated this type of therapy reported ten cases in which patients were treated with papaverine. One failure was unexplained and two were due to the long period elapsing between the onset of embolism and treatment. Improvement in the seven remaining cases was satisfactory. Allen and

MacLean reported impressive improvement in one extremity and none in the other in a case in which the arteries of both extremities were occluded suddenly. If improvement follows use of papaverine, the injection can be repeated whenever there is evidence of failing circulation to the extremity. The temperature of the environmental air, that is, the room temperature, should be kept at about 32.2°C . (90°F). Hot packs may be applied continuously to an extremity not involved or to the involved extremity *proximal to the embolus*, as both procedures should produce vasodilation. Intermittent venous occlusion may help. An ordinary sphygmomanometer cuff placed well proximal to the site of occlusion may be alternately inflated to diastolic blood pressure and deflated, at two-minute intervals for several hours. The Sanders oscillating bed, which performs postural exercises for the patient, may help, particularly if treatment is carried out in a warm room. Short wave diathermy may produce vasodilation. Electromagnetic induction by means of a cable arranged in a pancake formation over the lumbosacral area is a superior method.

The use of intermittent negative and positive pressure, as described by Herrmann and Reid, has been very successful in their hands and should be used if a machine is available. On the assumption that one of the chief requisites for a favorable outcome is the induction of collateral arteries to assume a heightened function of transportation of blood, spinal anesthesia may be tried when the lower extremities are involved, as Emmett has shown that this procedure produced maximal vasodilation. Brachial plexus block may produce similar effects in the upper extremities. General anesthesia may be used, if the condition of the patient permits, for the same reason that spinal anesthesia may be of value, as Craig and Horton have shown that general anesthesia produces maximal vasodilation. Sympathectomy likewise produces maximal vasodilation, as shown by Brown and Adson, Baldes, Herrick and Essex and is of value in sudden arterial occlusion, as shown experimentally by Mulvihill and Harvey; but ordinarily, the condition of the patient does not warrant such a major operation. If the procedures outlined, exclusive of sympathectomy, do not produce a rapid improvement in the circulation, surgical removal of the clot should be considered when occlusion is due to an embolus. As in the treatment of diabetic coma, constant attendance of a physician is required until the situation is relieved or the unfortunate

outcome is definitely established. This duty cannot be delegated to nurses or relatives judiciously. If the diagnosis is made promptly and the treatment outlined is carried out with celerity and constant attention we believe the results will be much better than they are when less rational or haphazard regimens are carried out.

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CHAPTER LVI

THROMBOPHLEBITIS

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Under the term thrombophlebitis are included a number of different diseases of the veins which produce a rather wide variety of clinical phenomena but which exhibit the common pathologic lesions of thrombosis and varying degrees of inflammatory change in the various coats of the wall of the vein. It is extremely rare to find a phlebitis without thrombosis except as a part of some more widespread inflammatory lesion. Equally rare is venous thrombosis that does not produce some inflammatory change in the wall of the vein at some stage of its evolution or involution.

ETIOLOGY

Although a great deal of work has been done on the subject our knowledge concerning the causation of many cases of thrombophlebitis is still very imperfect. Three hypotheses have been evolved: (1) That the primary disturbance lies in some lesion of the wall of the vein giving rise to both the inflammatory changes and to the intravascular thrombosis; (2) that the thrombosis is primary and is produced essentially by stasis of the blood stream and adherence of platelets to the intimal coat and that subsequently there is an inflammatory reaction in the wall of the vein to the thrombosis; (3) that a similar chain of events follows a primary thrombosis but that the thrombus occurs as the result of alterations in the physical properties or chemical constituents of the blood itself. Clinical observations on the various types of thrombophlebitis in different cases have been used to support each of these three hypotheses and it is quite possible that each mechanism may be the sole or predominant factor in certain cases. It is also possible that a combination of all three factors may be necessary to produce the lesion in other cases. Experiments on animals have not shed much light on the subject because it is very difficult to produce experimental thrombosis in animals and observations on thrombosis in blood flowing through

(1651)

extracorporeal chambers introduce factors that may not exist when the blood flows through the human veins. They do suggest however that the deposition of platelets may be a primary factor in certain types of thrombophlebitis.

From the clinical standpoint one may divide the various types of thrombophlebitis into four groups:

I Local that is attributable to known direct chemical mechanical infectious or suppurative trauma or occurring in diseased veins such as varices. In this group the evidence favors a primary lesion of the wall or intima of the vein as the essential factor.

A Chemical Thrombophlebitis The most outstanding example of this condition is the thrombophlebitis produced as the result of the injection of various sclerosing solutions into varices. These solutions produce injury to the intimal coat which is followed by thrombosis and phlebitis. Solutions commonly used are sodium morrhuate, sodium ricinoleate, quinine and urethane and hypertonic solutions of glucose and of sodium chloride. A similar type of thrombophlebitis may occur accidentally as a result of intravenous injection of various drugs and of solutions used in diagnosis. It has been observed following the injection of the mercurial diuretics, the various arsenicals, bromsulphalein, the iodides that are used in excretory urography and slightly hypertonic solutions of glucose and sodium chloride. Sensitiveness of the intima of the veins to these chemical solutions varies in different individuals. The lesions of chemical thrombophlebitis are usually fairly well localized although they may extend a considerable distance both distally and proximally from the site of injection.

B Mechanical Thrombophlebitis Under this category are included those types of thrombophlebitis that follow gross mechanical injury and originate at the site of the injury. The thrombophlebitis may extend a considerable distance from this point. A special type of traumatic thrombophlebitis is the so called axillary thrombophlebitis caused by strain or effort, a comparatively rare condition seen usually in the right arm of young to middle aged healthy men. It follows definite although sometimes minimal trauma to the axillary vein due to muscular effort with the arm in the abducted position. It has been suggested that rupture of the subclavian axillary valve is responsible.

C Local Inflammatory Thrombophlebitis In this group can be included a large number of lesions usually of the smaller veins or venules which occur as part of inflammatory lesions without suppuration. Thrombosis may occur in varying degrees but the lesions are rarely extensive and can be considered more as a part of the inflammatory disease than of a true thrombophlebitis. Such lesions are seen in association with erythema nodosum, tuberculosis and tuberculids, gummas and many other inflammatory processes of known and unknown origin.

D Suppurative Thrombophlebitis These lesions occur as the result of involvement of the wall of a vein by a severe suppurative disease. Subsequently an inflammatory infectious thrombus is produced; this contains bacteria which are discharged into the blood stream and produce septicemia and pyemia. Such a lesion is thus serious and may threaten life from dissemination of the bacteria and the development of metastatic infection. A typical example is the suppurative thrombophlebitis of the jugular vein occurring as a complication of suppurative mastoiditis. Suppurative thrombophlebitis is also seen in the portal vein and occasionally in the iliac veins or their branches as a result of intraabdominal infections. When suppurative thrombophlebitis is present there is usually a high fever of the septic type which may be accompanied by recurrent chills.

E Varicose Thrombophlebitis Spontaneous thrombophlebitis may occur in varicose veins. In many cases there is a minor injury to the vein or constriction from a bandage or garter above it. Focal or local infection may be a factor. Histologic studies of varicose veins usually show evidence of definite disease of the intima as well as the media and it is surprising that spontaneous thrombosis does not occur more often. In some cases varicose thrombophlebitis occurs as a complication of operations, childbirth and infectious disease. Varicose thrombophlebitis may remain as a fairly localized condition or extend into other veins.

II Hematogenic Thrombophlebitis When thrombophlebitis occurs spontaneously in patients with blood dyscrasias it seems logical to infer that it is caused by some change in the physicochemical properties of the blood and to consider that the thrombus is primary and the phlebitis is secondary. A number of writers in the nineteenth century noted the frequency with which thrombophlebitis complicated chlorosis. It is also one of the commoner complications of polycythemia vera. It has been

observed in various leukemias and in pernicious anemia particularly during the early period of active treatment

III Secondary (Complicating) Thrombophlebitis This comprises the largest group of cases encountered and is the group in which the exact causation and pathogenesis of the lesion is most obscure. In the great majority of cases the lesions occur in the veins of the lower extremities. Since a common denominator of most of the conditions that are complicated by thrombophlebitis is rest in bed and since it is known that this results in slowing of the circulation of the lower extremities it is in this group that many observers have considered venous stasis to be the primary causative factor. However, the other factors such as changes in the physicochemical properties of the blood and local lesions of the vein may be equally necessary for the formation of the thrombus. It remains difficult to understand how thrombophlebitis can be produced without some lesion or injury of the endothelium as a starting point. Although bacteria have been cultured from thrombi in certain cases their significance as etiologic factors has never been established and in the majority of instances no pathogenic organisms have been obtained. Cases of secondary thrombophlebitis can be divided roughly into five groups:

A Postoperative Thrombophlebitis This occurs after approximately one per cent of all operations and after approximately 16 per cent of operations where laparotomy is performed. Certain other predisposing factors seem to have been definitely established. It occurs more commonly in the aged, in the obese, in patients who have heart disease, carcinoma, active infections or blood dyscrasias (particularly anemia) and in those who have varicose veins or who have had previous thrombophlebitis particularly of recent origin. Operations that have a comparatively high incidence of postoperative thrombophlebitis are abdominal hysterectomy, gastric and intestinal resection and splenectomy. Since splenectomy is often done because of blood dyscrasias it has been felt that in these cases changes in the blood that may occur postoperatively, particularly increase of the concentration of thrombocytes, may be a definite factor. Other factors that have been considered to play some part in the development of postoperative thrombophlebitis are trauma to tributaries of the iliac veins particularly during pelvic operations, compression of the veins of the lower part of the abdomen and upper part of the thighs by tight

bandages following laparotomy, blood transfusions with imperfectly matched blood during the postoperative period, the intravenous administration of large amounts of fluids of various types and pressure on the legs, particularly the calves either during operation or during the postoperative convalescence. However, these factors will not explain all cases, since thrombophlebitis occasionally occurs in comparatively young otherwise healthy individuals after operations where none of these factors are present. It is extremely rare before puberty and comparatively rare in the second and third decades of life.

B Postpartum Thrombophlebitis This occurs after 0.4 to 1 per cent of deliveries. There is statistical evidence to show that it is commoner following difficult labor, cesarean section and instrumental delivery, also, that the incidence is higher in cases where puerperal sepsis is or has been present and in patients who have varicose veins or who are obese. It has been assumed that mechanical or infectious trauma to pelvic veins may form a locus for the development of an extending thrombosis but, as in postoperative thrombophlebitis, it is difficult to determine the factors responsible for the lesion in all cases.

C Thrombophlebitis as a Late Complication of Severe Injuries This may occur at a considerable interval after the injury (5 to 30 days) in patients who are kept in bed. The lesion is often in a large vein quite remote from the site of the injury. There is some analogy between these cases and cases of postoperative thrombophlebitis.

D Thrombophlebitis Complicating Infectious Diseases This has occurred following almost all types of infection. Statistics from a large series of cases have given the incidence in typhoid fever as approximately three per cent and in pneumonia as approximately 0.6 per cent. In these two conditions it usually occurs rather late in the course of the disease at least two weeks after the onset and often during the period of convalescence. Thrombophlebitis has also been noted as a complication of influenza, acute tonsillitis and pharyngitis and in these conditions it has usually appeared relatively early in the course of the disease, namely from the second to the fourteenth day. Other acute and chronic infectious diseases that have been complicated by thrombophlebitis are pyelonephritis, chronic ulcerative colitis, acute appendicitis, pelvic inflammatory diseases, undulant fever, the exanthems and many types of localized infection throughout the body. While in some of these cases the lesion

has appeared after the patient has been at rest for some time and may be quite asthenic others have occurred so early in the course of the disease as to suggest some relation to the infectious process itself or at least to the systemic febrile reaction. However it has not been possible to prove that this thrombophlebitis is a metastatic infectious lesion.

E Thrombophlebitis Complicating Noninfectious Systemic Diseases
Of these the greatest incidence has been noted in carcinoma and heart disease particularly with congestive failure. It has been thought that stasis of the blood stream as a result of congestion of the circulation or general cachexia has been in part responsible. Other diseases in which thrombophlebitis has been seen as a complication although rarely are exophthalmic goiter diabetes mellitus gout brain tumor and ureteral lithiasis.

IV Primary Thrombophlebitis In this group I have placed those cases where thrombophlebitis develops in the absence of any known injury to the vein where operation has not been performed where delivery has not occurred and where there has been no evidence of infection blood dyscrasias or systemic disease. There are three groups.

A Thromboangitis Obliterans Thrombophlebitis occurs in this disease in approximately 40 per cent of cases. The causes are still obscure and have been discussed elsewhere. It may be said that cessation of the use of tobacco has been followed in some but not all cases by cessation of the development of further episodes of thrombophlebitis.

B Recurrent Idiopathic Thrombophlebitis (Thrombophlebitis Migrans) There are many aspects of this condition which suggest that the lesion is the same as in thromboangitis obliterans. In occasional cases followed for long periods arterial lesions typical of thromboangitis obliterans have ultimately developed but in the majority the disease is confined to the veins just as in some cases of thromboangitis the lesions are confined to the arteries. Also large veins are affected much more commonly than in thromboangitis obliterans. It has been the opinion of several observers that focal or latent infections are common in this condition and their treatment or removal has resulted in cessation of the attacks. However efforts to culture any organism from the excised veins containing acute lesions have failed. The disease is predominantly seen in men—88 per cent. The average age in one series was 40 years.

and 80 per cent of the patients were less than 50 years old. Twelve per cent only were Jewish.

C. Idiopathic Thrombophlebitis of the Nonrecurring Type: In these cases the thrombophlebitis usually involves large veins of the lower extremities in patients who are otherwise healthy and in the majority of instances it occurs as a single episode. It has many of the same clinical features as the secondary or complicating thrombophlebitis. No significant predisposing factors in age and sex have been noted and so far there is no clue as to causation.

Finally, it may be said that in certain individuals there seems to be a predisposition for thrombophlebitis to develop under various circumstances. For example, patients have been seen whose veins seem to be very vulnerable to chemical injury and who have a history of having had thrombophlebitis following infectious diseases, operation and childbirth at various times. Also, it has been observed occasionally that a number of members of a certain family have been very susceptible to primary and secondary thrombophlebitis.

PATHOLOGY

Knowledge concerning the pathologic processes involved in thrombophlebitis is based on isolated pictures from necropsy and biopsy specimens, venography and a limited amount of experimental studies on animals. The pathogenesis of the lesions is therefore incompletely known, particularly in the early stages, which are the most important.

Common to all types of thrombophlebitis is pathologic evidence of thrombosis and inflammatory reaction in various coats of the venous wall. The fresh thrombus in large veins is usually lamellated and contains numerous thrombocytes, particularly in the layers in contact with the wall of the vein and then irregularly alternating layers of erythrocytes and fibrin with more thrombocytes, fibrin and leukocytes. This suggests that the evolution of the thrombus occurs layer by layer, yet there is usually little difference in appearance between the layers, so that it probably takes place in a relatively short time. In many instances a thickened portion of the intima with proliferation of the endothelium is found even in early lesions at some point in the affected vein. It is hard to be certain whether this is of considerable age or is an acute lesion. Organization of the thrombus takes place early, probably within 24 hours, certainly within 48 hours. In large thrombi the thrombus undergoes

involution during the next few weeks by a process of partial fibroplastic organization and partial liquefaction. The relative amounts of organization and liquefaction vary greatly in different cases but there is usually some permanent reduction of the lumen of the vein by fibrous tissue with bands extending across the lumen and layers adherent to the original intimal coat. These may be extensive and produce marked obstruction or they may be minimal. Thus after an attack of thrombophlebitis there is nearly always some restoration of function of the vein but it is usually incomplete.

The inflammatory reaction in the intimal, medial and adventitial coats of the veins varies greatly in degree in different cases. It has been said (Homans) that there is usually obstructive involvement of the perivenous lymphatics during the acute stage. One can see all types of inflammatory cells: leukocytes, lymphocytes and fibroblasts with congestion of capillaries in and around the venous wall but the fibroblast is the dominant cell after the lesion is a few days old. Permanent fibrosis of the wall of the vein and the adventitia may result.

There are certain variations in the pathologic picture in certain types of thrombophlebitis. In suppurative thrombophlebitis there is an intense inflammation of the venous wall with the leukocyte as the dominant cell. Also the thrombus contains many leukocytes and in certain regions it softens to become an abscess. Bacteria are frequently seen in these suppurative softenings. The intense inflammatory lesion may extend some distance from the original focus or abscess. In chemical thrombophlebitis there is a rather marked proliferation of the intima and a rather extensive cellular organization of the thrombus. In varicose thrombophlebitis there is usually thickening and degeneration of the intimal coat in addition to the marked thickening and fibrosis of the medial coat.

In the hematogenic types of thrombophlebitis the thrombus is more uniform in its early stages and organization is comparatively minimal and consists of rather acellular fibrous tissue. Inflammatory reaction in the wall of the vein is also minimal. A similar picture is seen in thrombophlebitis occurring in the cachectic states such as carcinoma and in congestive heart failure.

In primary thrombophlebitis—both the recurrent idiopathic type and thromboangitis obliterans—the lesions are segmental and involve predominantly small and medium sized veins. Here the fibroplastic reaction

is extreme both in and around the venous wall and in the thrombus. As a rule very little restoration of the lumen takes place. Even in very early lesions seen at biopsy the fibroblasts are closely packed together and often part of the occlusion of the lumen seems to be due to extensive proliferation of endothelial cells rather than to thrombosis. Giant cells may be seen in the more acute lesions.

PATHOLOGIC PHYSIOLOGY

The essential disturbance of physiology in thrombophlebitis is obstruction of venous blood flow. Owing to the extensive anastomosis of superficial veins and the presence of the two saphenous systems in the legs and the median basilic and median cephalic systems in the arms involvement of one of these veins or their smaller tributaries does not definitely embarrass the circulation from the limb. However when large trunks such as the iliofemoral axillary or the inferior vena cava are involved and obstructed by a thrombus that extends a considerable distance the distal venous pressure at heart level may be quadrupled. With the patient in the erect position the pressure may approach diastolic arterial pressure. This results in intense congestion of venules and capillaries and subsequently in transudation with edema. The role of the obstruction of the perivenous lymphatics in the formation of edema has been debated. *Homans* claiming that this lymphatic obstruction is the main factor in the production of the edema. However most of the swelling of the limb particularly in the early stages of the disease is due to extreme capillary congestion rather than to actual edema. It has been argued that because ligation of a large venous trunk did not produce edema therefore the edema could not be due to venous obstruction but in such an instance there is also little congestion. Also a thrombus several inches long produces much greater venous obstruction than a ligature because of coincident blockage of collaterals.

During the acute stage of obstruction of the iliofemoral vein the circulation is maintained through collateral veins which pass across from the superficial veins of the upper part of the thigh and lower part of the abdomen to the opposite side of the body through the abdominal wall to theazygos and mammary systems and through the pelvic plexuses to the opposite internal iliac vein. As the thrombus undergoes involution the pressure in the veins of the leg distal to the obstruction gradually falls but rarely to normal. The collateral veins gradually become depend

ing on their inherent strength and on how much of the blood from the limb they have to carry. In some cases huge varices are developed in these collateral veins (Fig 1). Following assumption of the erect posture after an iliofemoral thrombophlebitis there is an additional increase in



FIGURE 1 Dilated tortuous superficial abdominal and thoracic veins in old case of thrombophlebitis of inferior vena cava infrared photograph

the venous pressure in the distal veins of the leg. They may gradually dilate, varices may develop and the venous system may become incompetent producing chronic static edema. Chronic edema does not develop as often after obstruction of the axillary vein, probably because orthostatism has much less effect on increasing the venous pressure.

CLINICAL SYMPTOMS AND SIGNS

If one considers thrombophlebitis as an acute inflammatory lesion with associated obstruction of a vein the clinical phenomena are easy to understand. Pain and tenderness vary with the severity of the phlebitis and the degree of congestion of distal parts of the limb. Swelling with or without edema is associated with congestion and is seen only where there is involvement of a large venous trunk. Constitutional reac-



FIGURE 2 Primary thrombophlebitis involving superficial veins of lateral side of foot

tions such as fever, tachycardia and malaise are variable even in cases with apparently the same degree of local involvement. Chills do not occur and the temperature rarely rises over 39°C (102°F) except in the suppurative types where the constitutional symptoms are similar to those of septicemia from any source. As the acute phase of the lesion passes, persistent symptoms are nearly always the result of residual venous insufficiency and congestion. With our present knowledge it is easiest to consider the symptoms and signs of thrombophlebitis from the standpoint of the location of the lesion.

Thrombophlebitis of superficial veins, tributaries of the saphenous systems or small cutaneous veins is usually of the primary type, less commonly secondary to certain infectious diseases and occasionally, although rarely seen in cachectic states and blood dyscrasias (Fig. 2). The lesions are often multiple and appear as red, moderately painful, tender, raised

regions in the skin. In very small veins these may be circular but they are usually linear and can be felt as firm cordlike segments in the course of a visible vein. Constitutional symptoms are rare. The inflammatory reaction undergoes involution in from 7 to 18 days but the thrombosed vein can often be felt for a much longer period. In rare instances in the



FIGURE 3. Thrombophlebitis of long saphenous vein with considerable periphlebitis primary idiopathic type. Infrared photograph. Note prominence of long saphenous vein below lesion.

presence of arterial insufficiency necrosis of the skin occurs over the lesion (necrotizing phlebitis). The lesions are apt to recur periodically in crops and may extend by segments to larger veins.

Thrombophlebitis of the long and short saphenous veins, the median basilic, the cephalic and varices is easily recognizable as these veins are fairly large and fairly superficial (Fig 3). The periphlebitic reaction

varies but is usually definite and the vein can be felt as a firm cord. All types the local hematogenic primary and secondary may occur in these veins. Edema is rare but may occur in mild degree if the lesion is extensive and if the patient is ambulatory during the acute stage. Constitu-



FIGURE 1. Bilateral femoral thrombophlebitis—necrotic acute stage infrared photograph. Note edema below knee. Enlargement of thigh side to congestion.

tional reactions are usually mild or absent. Thrombophlebitis of the short saphenous vein is one of the *commonest* of the postoperative types and any patient who develops pain in the calf of the leg during the postoperative convalescence should be examined carefully for short saphenous thrombophlebitis. The lesion may extend into the femoral vein.

Thrombophlebitis of the lower femoral and popliteal veins usually produces deep tenderness and pain along the course of these veins and often some transient swelling and congestion of the lower part of the leg and the foot with mild constitutional symptoms.

Iliofemoral thrombophlebitis (milk leg phlegmasia alba dolens) usually produces a typical clinical picture (Figs 4 and 5). The majority of



FIGURE 5 Acute iliofemoral thrombophlebitis complicating chronic ulcerative colitis: infra-red photograph: superficial veins are distended in spite of elevation of leg.

cases are of the secondary or complicating type. The onset is usually sudden although it may follow a previous more distal thrombophlebitis or an embolic episode. Pain may be moderate to severe and is usually felt along the course of the affected vein or in various regions throughout the limb. Swelling is almost always present and may be extensive, involving the entire leg and thigh. The superficial veins are prominent and distended and the skin may be diffusely or locally cyanotic. Constitutional symptoms: fever (up to 39°C — 102°F), tachycardia and mild malaise are usually but not always present. The temperature of the skin of the leg varies. It may be slightly greater or slightly less than that of the opposite extremity but it is usually not greatly changed. Tenderness in

Scarpa's triangle is almost always present and is a valuable diagnostic sign. In many cases the thrombosed femoral vein can be palpated. Tenderness in the popliteal space and along Hunter's canal is usually present. The initial congestive swelling of the leg is often followed within a few days by edema which can be pitted by pressure. In a few cases where the onset is sudden there is spasm of the femoral artery with fall in the temperature of the skin and disappearance of peripheral arterial pulsations but this is the exception rather than the rule and is usually a transient phenomenon.

A very similar clinical picture takes place in the arm as the result of an acute axillary or subclavian thrombophlebitis although the swelling is usually less marked. The thrombosed axillary vein can usually be felt.

COMPLICATIONS AND SEQUELAE

The complication of thrombophlebitis that is most feared is pulmonary embolism. However there is considerable evidence both pathologic and clinical to indicate that a thrombus only breaks off and becomes an embolus very soon after its formation probably within a few hours certainly within a few days. Many fatal pulmonary emboli occur without any clinical evidence of thrombophlebitis. In many cases where there is nonfatal pulmonary embolism the thrombophlebitis follows rather than precedes the embolism. In a large series of cases of postoperative iliofemoral thrombophlebitis fatal pulmonary embolism occurred in only five per cent. In half of these it occurred within four days after the onset and in the other half it was found to have its origin from an unrecognized fresh thrombosis in the opposite iliofemoral vein. Histologic examination of pulmonary emboli shows absence of organization and organization of venous thrombi takes place fairly rapidly after their formation. It is probable that in a case of clinically recognizable thrombophlebitis embolism may occur only if the thrombosis extends to another larger and more proximal vein or if a fresh thrombus forms in a distant vein or rarely if the progress of organization is very slow (usually in ecthetic states). Hence the actual problem of prevention of embolism in thrombophlebitis is the problem of prevention of further thrombosis. Those few cases of secondary thrombophlebitis in which there are successive episodes of thrombophlebitis in various veins interspersed with episodes of pulmonary infarction are apt to terminate with fatal embolism. The inci-

dence of embolism in recurrent idiopathic thrombophlebitis is approximately 12 per cent, of fatal embolism 7 per cent.

Chronic venous insufficiency of the limb with its various manifestations is a serious complication of iliofemoral thrombophlebitis. It is often seen in patients with congenitally weak veins, in those who have previously had varices and in those who are obese. It is manifested first by edema, which accumulates during the day and disappears at night. Later the edema becomes chronic, superficial varices may gradually develop and there may be diffuse aching pain in the muscles after prolonged walking or more particularly after prolonged standing. Finally, more severe and disabling complications such as chronic indurated cellulitis, eczema of the skin and ulceration of the skin may appear.

Osteoporosis of the foot and mild degrees of muscular atrophy of the leg are seen occasionally as complications of thrombophlebitis but they are almost always associated with prolonged rest in bed or a prolonged period of disuse of the limb.

Postphlebitic neurosis is a real entity and has been described by Allen and Brown. The patients are almost invariably nervous women who have had a prolonged period of rest in bed as part of treatment and who have been impressed by the possibility of permanent disability or pulmonary embolism. The symptoms are weakness of the limb and pains of rather widespread distribution. The objective evidence of chronic venous insufficiency is usually minimal or absent.

DIAGNOSIS

Superficial thrombophlebitis involving small veins may have to be distinguished from erythema nodosum, nodular syphilids, and nodular tuberculids. The tendency of the lesion to a linear rather than a circular shape, its smaller size, lack of ulceration and comparatively rapid involution are distinguishing features.

Acute iliofemoral thrombophlebitis may have to be distinguished from acute arterial occlusion. In the latter condition the pain is apt to be more severe, the limb is pale, rather than cyanotic, the superficial veins are collapsed, the skin of the foot is cold and arterial pulsations are absent. The diffuse lymphangitis and cellulitis of the leg of the erysipelatous type, an increasingly common disease, should be easily distinguished from acute iliofemoral thrombophlebitis because the skin is

red, hot and diffusely tender. The veins are not distended and constitutional reaction is usually severe, with chills, high fever ($40^{\circ}\text{C}.$ — $104^{\circ}\text{F}.$) and much malaise.

Chronic venous insufficiency of the leg as a result of old thrombophlebitis may have to be differentiated from chronic lymphedema. In the latter the swelling is more brawny, superficial veins are not distended, the venous pressure is normal and the skin is thickened and firm. Some types of lymphedema are characterized by the gradual development of a painless, swollen leg while in postphlebotic edema one can almost always elicit the history of the acute episode.

TREATMENT

The treatment of thrombophlebitis can be divided into (1) preventive measures, (2) treatment during the acute stage, (3) prevention of complications and (4) treatment of complications.

Although certain principles of treatment apply to all the types of thrombophlebitis, there are special considerations that apply only to certain etiologic types.

Local Thrombophlebitis: The treatment of chemical thrombophlebitis is very simple. Rest of the limb and the application of warm wet packs for a few days is usually sufficient. Pulmonary embolism is very rare. Some patients apparently have easily injured veins and are very prone to develop chemical thrombophlebitis after intravenous injection of various chemicals. If this is known, the solution to be injected should be made as nearly isotonic as possible or should be mixed with an equal or greater volume of the patient's own blood before injecting and venipuncture should be made with as little trauma as possible. In varicose thrombophlebitis of spontaneous or secondary origin the treatment with rest and warm wet packs is usually all that is necessary and can be discontinued as soon as the periphlebotic reaction has subsided. Embolism is also rare in these cases unless the thrombosis extends to the main venous trunks, as there is usually a constriction at the proximal end of the varix. In some instances where large superficial varices are affected, involution of the thrombus is very slow and surgical excision of the entire thrombosed vein will shorten the period of disability considerably.

The treatment of suppurative thrombophlebitis is largely surgical. As soon as the diagnosis is made the vein should be ligated, if possible at

a point just proximal to the lesion. If an abscess forms in the affected segment, incision and drainage will usually be necessary. In hemolytic streptococcal bacteriemia secondary to suppurative thrombophlebitis, sulfanilamide therapy has been quite effective.

Hematogenic Thrombophlebitis: In these types the prevention consists in the treatment of the blood dyscrasia. Active treatment is essentially the same as is discussed in the following paragraph.

Secondary Thrombophlebitis: The prevention of postoperative, postpartum and posttraumatic thrombophlebitis and those types that complicate infections and constitutional and cardiac disease is a problem that has not yet been solved. It is an important problem because it is also the only direct attack on the prevention of pulmonary embolism. A number of plans have been advocated but results have been difficult to evaluate because of the comparatively small incidence of both thrombophlebitis and embolism and the necessity for using any one plan in several thousand cases before any conclusions can be drawn.

Too little is known about the nature or importance of local lesions of the veins as causative factors to permit of much therapeutic attack from this angle. However, avoidance of trauma to veins as far as possible during surgical or obstetric procedures can be reemphasized and also *avoidance of pressure on the calves of the legs and the groins both then and during convalescence.*

Most of the preventive measures have been directed toward minimizing the venous stasis in the legs. Frequent exercises performed several times daily by the patient, massage of the legs for periods two or three times a day, and elevation of the legs for a period of several days following operation have been advocated and undoubtedly improve venous circulation to some extent. It is probable that there is less risk of thrombophlebitis and embolism if the period of postoperative or postpartum rest in bed is made as short as possible.

Walters advocated the use of thyroid extract and this has been shown to increase the rate of flow of venous blood in the legs in postoperative convalescents definitely. However, it is necessary to individualize the dosage carefully for each patient and the use of thyroid extract has only been partially effective in reducing the incidence of postoperative thrombophlebitis and embolism.

The most logical preventive attack would seem to be reduction of the coagulability of the blood. Recently the production and use of a purified nontoxic heparin by Best and Murray and their coworkers^{24, 25, 26} have shown that this is possible. At present this heparin is expensive and its effect exists only while it is given continuously intravenously, but it can be given safely and apparently definitely prevents thrombosis while it

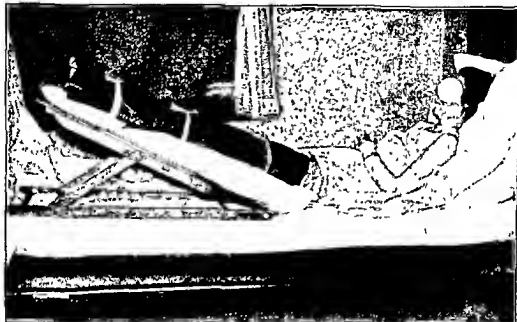


FIGURE 6 Frame for elevation of leg in treatment of acute iliofemoral thrombophlebitis. Hot wet pack has been applied.

is being given. As yet it is not practical for routine use but, where embolism has occurred once, there is a great enough chance of further thrombosis and embolism to justify giving it continuously for at least a week.

The treatment of secondary iliac or femoral thrombophlebitis during the acute stage should provide: (1) All possible aids to the venous circulation through the collateral veins; (2) aids to hasten normal involution of the lesion; (3) means for prevention of extension of thrombosis into other veins; (4) means for prevention of fear on the part of the patient. As much can be accomplished by simple procedures as by complex methods. The affected limb should be elevated so that it forms an angle of at least 30 degrees with the horizontal (Fig. 6). Adequate hot, wet packs should be applied from the ankle to the groin. The skin is

covered with a thin layer of petrolatum in order to prevent ulceration. Over this is wrapped a thin layer of gauze. Then portions of blanket material which have been soaked in hot water and wrung out are wrapped around the leg loosely. The entire pack is surrounded by a rubber sheet and hot water bottles are placed on the outside surface of the rubber sheet in order to conserve the heat. A new pack should be applied every hour if necessary to keep it hot. Care must be taken not to have the pack hot enough to burn the skin.

There is no justification for use of cold packs at any time inasmuch as application of cold produces vasoconstriction and more venous stasis than already exists; therefore, it favors extension of thrombosis to other veins and retards normal involution of the lesion.

Use of dry heat has not been as successful as use of hot wet packs although the reasons for this are not clear. A congested skin with retarded circulation is burned easily and is burned more easily by dry heat derived from electric bulbs, hot water bottles or hot puls than by moist heat derived from hot wet packs.

Sedatives may be necessary for control of pain during the first or second day but rarely after this. Rest in bed, elevation of the affected limb and application of hot wet packs are continued until swelling and edema have disappeared from the leg, until the temperature has been normal for at least four days and until tenderness along the affected veins has disappeared completely. Usually treatment for 10 to 18 days is required to accomplish these objectives; at the end of this time the patient is allowed out of bed. There is no justification for keeping patients in bed for long periods inasmuch as this does not tend to prevent pulmonary embolism, does not prevent development of chronic venous insufficiency and tends to focus the attention of the patient on his disability.

Other procedures such as use of leeches, roentgen therapy, surgical enlargement of the femoral ring and splitting of the vascular sheath, use of diuretics, of iodides, sodium thiosulfate and special diets have been advocated for treatment of severe degrees of femoral and iliac thrombophlebitis but it has not been shown that they are superior in any way to the simple methods of treatment by elevation of the affected limb and application of hot packs and there are serious objections to some of them.

One of the most important aspects of treatment of iliac and femoral thrombophlebitis is that of management after the patient has been

allowed out of bed. This is also the phase of treatment that is most likely to be neglected. During the latter days of the acute phase of the disease when the patient is still confined to bed and the affected limb is elevated, the return circulation is adequate for this position but when the patient stands there is added to the residual partial obstruction of the venous trunk the factor of gravity with a great increase in the hydrostatic venous pressure. The complication of chronic venous insufficiency of the limb may be prevented in the great majority of cases by the immediate use of an adequate supportive elastic bandage or elastic stocking. Inasmuch as secondary complications occurring in the thigh are not to be feared, it is not necessary that the support extend above the knee. Furthermore, it is difficult, if not impossible, to apply a comfortable and efficient elastic support around and above the knee. The patient should begin to wear the elastic support when he is allowed out of bed for the first time.

Heavy elastic stockings, if made to measure, may fit well. Measurements should be taken when the leg is free of edema. The disadvantages of elastic stockings are that they do not always fit well, cannot be readjusted once they are made, are relatively expensive and do not give adequate support after two or three months of use. Cloth mesh bandages are rarely adequate.

The most efficient bandage is one made of pure solid gum rubber three inches wide and five yards long. Such a bandage should be applied over a white cotton stocking and care should be taken that the shoe completely overlaps the bandage around the heel and over the dorsum of the foot (Fig. 7). The advantages of such a bandage are that it will control the swelling and will support the veins even after the most severe type of thrombophlebitis has occurred, that it can be applied snugly, can be adjusted until comfortable, that it is relatively inexpensive and has excellent wearing qualities. The patient should be instructed regarding application of the bandage; it should be applied when he first gets up in the morning, should be worn continuously except when he is in bed at night, and should be removed and immediately reapplied twice during the day. After three months the bandage or stocking may be left off half a day, later for a full day if no swelling is noted; but if some swelling does appear, use of the bandage should be continued until this no longer happens. It is rarely necessary for the patient to wear the

bandage more than a year and usually not more than six months, if it is applied before any orthostatic edema has had a chance to develop

During the first few weeks after the patient has been allowed out of bed, he should sleep with his legs elevated on one or two pillows at



FIGURE 7 Heavy pure rubber bandage applied over white cotton stocking in treatment of iliofemoral thrombophlebitis after acute stage and when patient becomes ambulatory

the end of that time it is advisable for him to perform the so-called elevation exercises, namely, lying on the back, raising the feet in the air and going through the motions of riding a bicycle during alternate minutes for a period of 15 or 20 minutes, twice a day. Later, swimming is an excellent exercise for improving venous circulation

Treatment of secondary superficial varicose long saphenous and short saphenous thrombophlebitis during the acute stage usually requires a shorter period of rest in bed. The criterion for allowing the patient up should be disappearance of local tenderness in the affected vein. Bandages or stockings are usually not necessary but if edema of the ankle appears after the patient is ambulatory a light bandage should be used.

Primary Thrombophlebitis Treatment during the acute stage should follow the same principles as were mentioned for the secondary types depending on the veins involved. Otherwise the chief problem is the prevention of further attacks or episodes for which no rules can be made that will fit all cases. Local excision of affected superficial veins has been effective in some but not all cases and should be considered where the lesion is progressing by contiguous segments. Elimination of focal infection has stopped the attacks in many cases. If the episodes continue in spite of this a course of injections of streptococcal vaccine can be given in gradually increasing doses but in amounts that will not produce systemic reactions. In some cases recurrences have ceased after a course of intravenous injections of typhoid vaccine sufficient to produce a moderate systemic reaction. Sulfanilamide has been used successfully in some cases where the lesions have been recurring rapidly. In thrombophlebitis obliterans the lesions of the veins are rarely of much clinical significance compared with the arterial lesions. It must be remembered that in some cases of recurrent idiopathic thrombophlebitis arterial lesions will develop.

Postphlebitic Neurosis As this is usually the result of prolonged rest in bed and fear of embolism or permanent disability it is wise to adopt an attitude of encouragement and to get the patient up as soon as possible. Patients and relatives of patients with thrombophlebitis should not be told that there is danger of embolism.

Chronic Venous Insufficiency When a patient is first seen with well-developed chronic venous insufficiency of the limb as the result of a previous thrombophlebitis the first step should be a short period of rest in bed to drain the leg of edema fluid. He should then be equipped with an adequate heavy support. It may be necessary for him to wear such a support the rest of his life but trial periods without it may be begun in a year. Ordinarily treatment of secondary varices by injection of sclerosing solutions is not advisable in these cases and will not help

symptoms or prevent further complications but occasionally it is advisable to destroy large localized varices particularly where they lie just proximal to ulcers. Chronic indurated cellulitis is best treated as early as possible by a period of several weeks of rest in bed and application of warm wet packs. Many stasis ulcers may be satisfactorily treated by the ambulatory pressure method of treatment (McPheeters) using a sterile gauze sponge then a rubber sponge over the ulcer and then applying an adhesive bandage or a nonadhesive rubber bandage. Almost all ulcers can be healed by putting the patient to bed with the leg elevated and applying warm wet packs of solution of boric acid or 0.5 per cent aluminum acetate to the ulcer. When ulcers are large healing can be hastened by using skin grafts after the base has become clean and covered with healthy granulations. Finally patients with chronic venous insufficiency should be instructed carefully regarding their problem the influence of position gravity and muscular activity on venous circulation the importance and principle of adequate leg supports and avoidance of trauma to the skin.

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NOTE Many of the articles mentioned in the list of references served as background in writing of this chapter and cannot be identified with specific portions of the text

failure Holman in 1923 after analyzing Halsted's cases determined that in the presence of small arteriovenous communications changes in the cardiovascular system never developed but invariably they did appear when the fistula was large. Harrison, Dock and Holman in 1924 produced arteriovenous fistulas experimentally in animals and found the blood flow through the lungs of such animals uniformly increased to an amount 100 per cent greater than the normal. Smith in 1931 found a reduction of 58 per cent in cardiac output and an increase of 120 per cent in the coefficient of utilization after repair of fistulas in cases in which cardiovascular symptoms occurred.

Diagnosis The diagnosis of an arteriovenous fistula usually is not difficult if the condition is suspected. In most of the cases attention will be directed toward an enlarged and swollen limb which may be mistakenly thought to be due to varicose veins. Closer inspection and palpation of the limb will reveal a pulsating tumor at some point along the larger vessels with an audible bruit and palpable thrill. The thrill and bruit are present throughout the cardiac cycle but are more prominent during systole than during diastole. There will be an increased temperature of the surface of the involved extremity particularly in the region of the fistula. Brannan's bradycardiac phenomenon of slowing of the pulse and temporary hypertension may be elicited by occlusion of the fistula. If a bruit is absent and there is a question as to the diagnosis a puncture of one of the regional veins will reveal arterial blood which is diagnostic of an arteriovenous fistula. Because the arterial blood is shunted directly into the veins there is usually a vascular deficiency distal to the fistula. The patient may complain of claudication and have symptoms of ischemic neuritis. Trophic changes, ulcer and even gangrene may develop in the lower part of the extremity. In cases of fistulas of longstanding the picture may be one mainly of congestive heart failure.

ILLUSTRATIVE CASE A man aged 51 years came to the clinic in September 1935 because of epigastric distress, gaseous indigestion and dyspnea of six months duration. The dyspnea had increased gradually so that he was unable to walk more than a block without severe distress. Swelling of the right leg had been present for three years. In the three months prior to admission he had noted increasing swelling of the left foot and leg.

In November 1922 the patient had been wounded while hunting deer. The bullet entered the left hip and traveled across the pelvis into

CHAPTER LVII

ACQUIRED ARTERIOVENOUS FISTULA, TEMPORAL ARTERITIS AND ANEURYSM*

By EDGAR A. HINES, JR., M.D.

ACQUIRED ARTERIOVENOUS FISTULA

Definition: Arteriovenous communications, short cuts or shunts between the smaller arteries and veins, form a part of the delicate mechanism which regulates circulation. However, when a large artery and vein communicate with one another, the dynamics of the circulation are profoundly disturbed, frequently with serious results. Large arteriovenous communications may be congenital or acquired. In the congenital form, the communications are usually multiple, whereas in the acquired form the communication is single, although Horton and Meyerding recently reported a case of traumatic arteriovenous fistula in which there were two communicating tracts some distance from each other. Congenital arteriovenous fistulas are considered in detail in the chapter on "Varicose veins with congenital anomalies of arteries and veins."

Etiology and Physiology: Acquired arteriovenous fistula usually results from trauma such as a bullet wound or stab wound. It is a relatively common condition. Callander, in 1920, tabulated 444 cases which had been reported in the literature up to that time and many reports of such cases have appeared since.

The deleterious effect which an arteriovenous fistula may have on the heart makes the early recognition of the condition of great importance.^{5,6} As pointed out by Lewis and Drury, when the fistulous opening is free, the characteristic signs of aortic reflex ensue in the arterial system, namely, high pulse pressure, capillary pulse, water-hammer pulse and so forth. The result is a train of events such as results from aortic regurgitation with the development of cardiac enlargement and eventually congestive

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Diagnosis The diagnosis of an arteriovenous fistula usually is not difficult if the condition is suspected In most of the cases attention will be directed toward an enlarged and swollen limb which may be mistakenly thought to be due to varicose veins Closer inspection and palpation of the limb will reveal a pulsating tumor at some point along the larger vessels with an audible bruit and palpable thrill The thrill and bruit are present throughout the cardiac cycle but are more prominent during systole than during diastole There will be an increased temperature of the surface of the involved extremity particularly in the region of the fistula Branham's bradycardiac phenomenon of slowing of the pulse and temporary hypertension may be elicited by occlusion of the fistula If a bruit is absent and there is a question as to the diagnosis a puncture of one of the regional veins will reveal arterial blood which is diagnostic of an arteriovenous fistula¹ Because the arterial blood is shunted directly into the veins there is usually a vascular deficiency distal to the fistula The patient may complain of claudication and have symptoms of ischemic neuritis Trophic changes ulcer and even gangrene may develop in the lower part of the extremity In cases of fistulas of longstanding the picture may be one mainly of congestive heart failure

ILLUSTRATIVE CASE A man aged 54 years came to the clinic in September 1935 because of epigastric distress gaseous indigestion and dyspnea of six months duration The dyspnea had increased gradually so that he was unable to walk more than a block without severe distress Swelling of the right leg had been present for three years In the three months prior to admission he had noted increasing swelling of the left foot and leg

In November 1922 the patient had been wounded while hunting deer The bullet entered the left hip and traveled across the pelvis into

the right inguinal region. He had recovered satisfactorily from this accident except for residual atrophy of muscles of the left calf and left foot-drop caused by injury of the left sciatic nerve. He was otherwise entirely well until 1932 at which time the right foot and leg began to swell. In March 1935 he first noted abnormal pulsation and thrill in the right femoral region.

The patient when seen for the first time at the clinic was obviously suffering from a severe degree of cardiac failure. He was orthopneic and there was marked edema of the lower extremities. There was great enlarge-



FIGURE 1. Comparison of the size of the heart. A. Before operation. B. One month after operation. (Hines & Waugh. Proc. Staff Meet. Mayo Clin.)

ment of the region of cardiac dullness and the edge of the liver was palpable 6 cm. below the costal border. The blood pressure in millimeters of mercury was 154 systolic and 76 diastolic. The pulse rate was 90 beats per minute. The right thigh was definitely warmer than the left and there was a definite thrill and bruit over the right femoral region. When the right femoral artery was closed by deep pressure the rate of the apex beat of the heart decreased from 90 to 60 beats per minute. A teleoroentgenogram revealed the transverse diameter of the heart to be 21 cm. and the diameter of the thorax 32 cm. (Fig. 1 A). It was felt that in spite of the poor condition of the patient an attempt should be made to repair the fistula. He was hospitalized and put on a regimen to produce dehydration. This included limitation of intake of fluids and the administration of diuretics. In less than one week 13.6 kg. (30 pounds) of edema fluid were removed and the patient's cardiac function was greatly improved.

Surgical exploration of the region was undertaken by Dr. Pemberton September 16, 1935. A longitudinal incision was made in the right in-

ginal region the inguinal ligament was divided and the external iliac and femoral vessels were exposed. There was an arteriovenous fistula about 2 cm in diameter between the femoral artery and vein exactly at the point at which the profunda femoris branched off from the main vessel.

About 1 cm above the inguinal ligament a tape was placed around the external iliac artery and another around the vein so that they could be used if necessary to control hemorrhage during the operation. These two vessels were huge measuring about 5 cm in diameter but were constricted as they passed below the inguinal ligament. The femoral artery and vein were exposed below the fistula and tapes were placed around them for emergency purposes. The femoral artery below the fistula was small but the vein was dilated in three or four times its usual diameter.

In an attempt to expose the communication between the artery and vein an opening was made in the femoral artery which necessitated its ligation just below Poupart's ligament. The artery was then opened through a longitudinal incision and the communication between the femoral artery and vein was exposed and sutured with silk. There was good retrograde bleeding from the distal ends of the femoral and profunda femoris arteries and these two vessels were ligated at their point of junction.

Excepting the fact that in the right calf there was severe pain of an ischemic neuritic type which lasted several days the patient made an uneventful convalescence and was dismissed from the clinic one month after operation. At the time of his dismissal the size of the heart had decreased greatly as compared with that prior to operation (Fig 1B). The blood pressure in millimeters of mercury was 130 systolic and 90 diastolic and the pulse pressure was normal. The pulse rate was 90 beats per minute. Pain and dyspnea on exertion did not occur and the patient could walk several blocks without difficulty.

Treatment. In every case of traumatic arteriovenous fistula an attempt should be made to repair the fistula surgically. Before attempting repair it is well to wait for three to six months after the inception of the fistula to allow time for establishment of collateral circulation. Also the delay makes dissection easier and permits subsidence of infection. The Moskowitz-Matis¹¹ hyperemic test is useful in determining the status of the collateral circulation. Such a test is carried out by elevating the extremity and allowing it to become as ischemic as possible. An elastic bandage is then applied in circular fashion from the digits to the level of the lesion. The artery proximal to the lesion is occluded by compression preferably by a clamp or by digital pressure. A tourniquet or inflated blood pressure

cuff may be used but has the disadvantage of interfering to some extent with the collateral circulation. The bandage is removed after five to ten minutes while the artery still remains occluded. The extent and rapidity of development of the hyperemic flush which follows removal of the bandage is an index of the efficiency of the collateral circulation.



FIGURE 2. Arteriogram showing fistula between femoral artery and vein. a Byd shot, b femoral artery, c femoral vein, d saccular enlargements in the femoral vein (Horton, *Am J M Sc.*)

If possible the site of the fistula should be determined by arteriography before surgical exploration is attempted (Fig. 2). The arteriographic demonstration of an arteriovenous fistula at the clinic was first carried out by Horton and Ghormley. Their technic is as follows. A local anesthetic agent is infiltrated around either the brachial or the femoral artery. A 20 gauge needle on a 20 cc syringe is inserted into the artery and the artery is closed either by the use of a blood pressure cuff if the injection is being made into the brachial artery or by digital pressure just proximal to the needle when the injection is being made into the

femoral artery. An injection of 10 to 12 cc of thorotrast is then made into the artery. The thorotrast is injected promptly and four or five roentgenograms are made in rapid succession while the artery is still closed. The interpretation of the films depends on the fact that when the injection is made into the normal arterial tree thorotrast does not appear in the veins in the first film after injection if the portion of artery proximal to the point of injection is kept closed. The demonstration of the thorotrast in the first film with the artery closed therefore is diagnostic of an arteriovenous fistula. The amount of filling by the thorotrast on the venous side is proportional to the size of the fistula.

No single surgical procedure is adaptable to all cases of arteriovenous fistula. The ideal procedure would be to excise or obliterate the fistulous tract allowing the lumen of the artery and vein to remain patent. It is important after careful dissection to correlate the anatomic findings with the condition of the collateral circulation before determining the operative procedure most applicable. Ligation of the artery proximal to the fistula alone is not satisfactory. This might relieve the load on the heart somewhat but usually it diminishes the circulation to the tissues below the fistula so greatly that gangrene results. Excision of a segment of the artery and vein including the communications and quadruple ligation has given satisfactory results in certain cases in which the ideal procedure of preserving the lumen of the artery and vein could not be performed.

TEMPORAL ARTERITIS

Temporal arteritis is a regional arteritis representing a clinical syndrome which is apparently distinct from periarteritis nodosa. It generally affects elderly persons and is characterized by an arteritis usually limited to the temporal arteries and is accompanied by moderate toxic symptoms particularly anorexia, malaise, fever, night sweats, loss of weight, anemia and leukocytosis.

This syndrome was first described by Horton, Magath and Brown of The Mayo Clinic in 1934. The first patient recognized as suffering from this condition was seen in 1931. Since that time eight patients who had temporal arteritis have been observed at The Mayo Clinic and several cases have been described in the literature by others.

Etiology. The cause of the peculiar process affecting the temporal arteries is unknown. In the carefully studied series recently reported by

Horton, Magath and Brown cultures made from the resected arteries in five cases gave negative results. Inoculation of animals gave negative results and studies of numerous microscopic sections failed to reveal the presence of the *Mycobacterium tuberculosis* and *Treponema pallidum*. Agglutination tests for typhoid, paratyphoid, undulant fever and tularaemia were negative. Although the appearance of the lesion pathologically is suggestive of an inflammatory process of low grade, the changes may be on a degenerative basis due to changes in the vasa vasorum. The advanced age of the patients so far observed particularly is suggestive of the possibility that degenerative factors are of importance in the development of the lesion.

Pathology: The characteristic pathologic picture is one of a chronic periarteritis and arteritis. The intima is greatly thickened and the media is necrotic in some regions. In the portions of the media in which repair is taking place, there is granulomatous tissue which contains numerous giant cells. Nodular regions along the adventitia consist of collections of round cells around the vessels of the vasa vasorum. The aneurysmal sacs, frequently associated with lesions of periarteritis nodosa, are not found in the lesion of temporal arteritis.

Diagnosis and Prognosis: This disease, so far, is known to afflict elderly persons only, without predilection for either sex. The presenting symptom is always headache, usually of a severe type and often worse during the night than during the day. Jarring of the head, coughing, sneezing and chewing greatly aggravate the pain. Accompanying the headache or shortly after its appearance, signs of an infection of low grade develop. Fever, malaise and exhaustion are outstanding. A mild leukocytosis usually is present. As the disease progresses a moderate anemia develops. From two to five weeks after the onset of symptoms the characteristic objective features of the disease namely, tortuosity, prominence and extreme tenderness of the temporal arteries, become evident. Along the course of the arteries small nodules can be palpated. As the process continues, the pulsation in the artery is diminished and eventually the lumen may be occluded. Usually, only the temporal arteries are involved although in one case which I encountered, the same process occurred in a section of the radial artery. In two cases encountered by Horton, Magath and Brown there were inflammatory, vascular lesions present in the ocular fundi.

The disease tends to be self limiting and runs a course of four to six months. Complete recovery resulted within two years after the onset of symptoms in all of the cases so far reported. During this time however the patients were more or less disabled because of the severe headache and unpleasant systemic reaction.

ILLUSTRATIVE CASE A married woman aged 69 years was admitted for the first time to the clinic in February 1935. Her chief complaint was pain which had been present for two months over her right eye. For six weeks the pain had been constant and had been projected from the right eye toward the right side of the head and into the neck and shoulder. Ten days before admission her temporal vessels on the right side had become noticeably engorged. Also she had complained of anorexia, loss of weight and nausea. She had experienced some fever and considerable general weakness. The general examination gave essentially negative results except for prominence of the temporal vessels and redness over the right temporal artery with severe tenderness along the course of the artery. During her stay of five weeks in the hospital the temperature by mouth ranged from 36.1 to 38.3° C (97 to 101° F) the pulse rate ranged from 70 to 110 beats a minute. The blood pressure on admission in millimeters of mercury was 145 systolic and 95 diastolic. Neurologic examination gave objectively negative results as did that of the cerebrospinal fluid. The number of leukocytes varied from 9000 to 14800 per cubic centimeter of blood. erythrocytes 4380000. The concentration of hemoglobin was 11.7 Gm per 100 cc of blood. Repeated urinalyses gave negative results. Likewise cultures of the blood and agglutinations for undulant fever, typhoid fever and paratyphoid fever gave negative results. Roentgenograms of the head and thorax were normal. A segment of the right temporal artery was removed for biopsy sections of which revealed a subacute arteritis and periarteritis with proliferation of the intima which almost occluded the lumen. There was much destruction of the media and many giant cells were present.

Treatment was started with potassium iodide giving as much as 50 drops of the saturated solution four times daily. This large dose was well tolerated. Codeine and aspirin were given for the relief of pain. The patient was given 0.3 Gm of neoarsphenamine intravenously each week. After the removal of the artery the headache was greatly improved. On the eighth day after admission the patient began to complain of pain in the left forearm and it was soon observed that an arteritis was developing in the left radial artery. The distal third of the artery became tender, red and thickened. A section of the artery was removed and the microscopic picture of the sections was similar to that of the portion of tem

poral artery previously subjected to biopsy but the process was more acute in the radial artery. Removal of the radial artery relieved the pain in the arm. At the time of the patient's dismissal 38 days after admission she did not have fever, her strength was much improved and the headache had for the most part disappeared. After returning home the patient continued to take the potassium iodide and a dose of 0.3 Gm. of neoarsphenamine was administered each week for six weeks. Six months after dismissal in a report from her physician it was stated that the patient was almost entirely relieved of symptoms and that she had been afebrile for three months.

Differential Diagnosis. Temporal arteritis should be distinguished from periarteritis nodosa because of the grave prognosis in the latter condition. The regional nature of the temporal arteritis contrasted with the more general involvement and the more severe systemic symptoms of periarteritis nodosa should serve to distinguish the two conditions. In the early stages of periarteritis nodosa the diagnosis is usually obscure because of the absence of involvement of large and visible arteries. If difficulty is experienced in the differential diagnosis a positive diagnosis of temporal arteritis can be made after biopsy of a portion of involved artery. Migraine should not be easily confused with temporal arteritis as in the latter case the headache is usually continuous and systemic symptoms soon occur. There may be some difficulty in distinguishing between temporal arteritis and a headache designated by Horton, MacLean and Craig as erythromelalgia of the head. In the latter condition the headache is of a throbbing type and there are distention and congestion of the vessels in the temporal region. However the distention and congestion occur only during the headache and the arteries are not tender and nodular as in cases of temporal arteritis. Furthermore the systemic signs of infection do not occur if the erythromelalgia type of headache is present.

Treatment. Relief of the distressing headache and general supportive measures are the main considerations in treatment inasmuch as the disease itself is self-limiting. If the administration of simple anodynes and opiates does not control the headache excision of the segments of the involved artery usually will give considerable relief. The administration of large doses of iodides has been of benefit in some of the cases.

ANEURYSM

General Considerations Aneurysms of the large arteries of the trunk and extremities have been recognized since the time of Galen. Cerebral aneurysms because of the obscurity of symptoms and lack of objective signs have been recognized only in comparatively recent times. Descriptions of the pathologic characteristics of aneurysm abound in the literature and etiologic factors have been considered at length but there have been few studies from the physiologic standpoint which is of great importance when therapy is to be considered.

All true aneurysms have at least one layer of the arterial wall forming the sac. False aneurysms are hematomas which result from rupture of the arterial wall. Aneurysms may be single or multiple. In the large arteries of the trunk aneurysms are usually single whereas in the cerebral arteries and arteries of the extremities they are frequently multiple. The etiologic factor and the difficulty of diagnosis are dependent on the situation of the aneurysm. The majority occur within the thorax. In the series of 596 cases of aneurysm at The Mayo Clinic which were reviewed by Mills and Horton the incidence according to situation was as follows: Head 24 per cent, thorax 56 per cent, abdomen 13 per cent and extremities 3 per cent.

Aneurysms may be classified according to their etiology as syphilitic, arteriosclerotic and congenital or mycotic or according to situation as intracranial, abdominal and so forth. The classification of aneurysms into different groups because of minor anatomic differences as to shape and form of the aneurysmal sac is of little practical importance. Of more importance is the situation of the aneurysm as regards collateral circulation and accessibility.

Etiology Anything that produces weakening of the wall of an artery may result in the formation of aneurysm. The situation of the aneurysm is a determining factor in its etiology. Aneurysms of the arch of the aorta are usually syphilitic inasmuch as it is this part of the vascular tree which is most commonly affected by syphilis. The farther the aneurysm is from the arch of the aorta the less frequently is syphilis an etiologic factor and the more important are arteriosclerotic changes and congenital defects. Good evidence of this is furnished in the series reported by Mills and Horton in which syphilis was the etiologic factor in 70 per cent of the cases of aneurysm of the thoracic aorta and in only

nine per cent of those of aneurysms of the abdominal aorta. Infection is an infrequent cause of aneurysms as the arterial wall is highly resistant to infection by encroachment from adjacent tissues. Embolic or mycotic aneurysms may be associated with bacterial endocarditis in which case the initial lesion is probably due to embolism of the vasa vasorum. Trauma plays an important rôle in the occurrence of aneurysms of the extremities and those developing after gunshot and stab wounds in other parts of the body. Congenital defects are of importance in aneurysms of the cerebral arteries and in the smaller arteries such as in the pulmar arch.

Pathologic Characteristics: The pathologic characteristics of an aneurysm depend on the extent and nature of the underlying lesion. The important change takes place in the *media* which is the main supporting part of the arterial wall. The weakening of the media results in a dilatation forming a sac which, in the diffuse type is covered by all of the layers of the arterial wall. In the saccular form, the process of dilatation disrupts the layers and both muscular and elastic tissue are replaced by fibrous tissue. As the blood stream is slowed, mural thrombi form on the wall of the sac and may result in complete occlusion. Closure by thrombosis is more likely to occur in the saccular type than in the diffuse type. The microscopic appearance of a section of the wall of the aneurysm will depend on the underlying etiologic factor.

Signs and Symptoms: Except for the observable pulsating mass and the bruit, aneurysms produce most of their characteristic signs and symptoms through pressure on contiguous structures. Consequently, the signs and symptoms are dependent on the situation of the aneurysm and are best considered from this standpoint.

Cerebral Aneurysm: The signs and symptoms of a cerebral aneurysm do not form a characteristic picture which can be recognized very often with certainty. However, more careful correlation of the clinical picture with the findings at necropsy has resulted in recognition of certain significant signs and symptoms which materially aid in making a correct diagnosis of a condition which was described in the early textbooks of medicine as being impossible of diagnosis ante mortem. Aneurysms may occur in any of the cerebral arteries but they are commonest in the arteries of the circle of Willis. Often the diagnosis cannot be suspected until rupture occurs with leakage into the subarachnoid space, presenting the symptoms of severe basilar headache, vomiting and drowsiness associated

with a stiff neck and a bloody spinal fluid. The sudden onset of a unique, severe headache in an old person who has hypertension always should be considered as due to a ruptured aneurysm until proved otherwise. When leakage or rupture has not occurred, the findings will depend on the size and situation of the aneurysm in relation to contiguous structures. The picture may be similar to that of a neoplasm, particularly in cases of suprachnoid aneurysm which give findings similar to those associated with basofrontal neoplasms, such as mental disturbances, changes in the visual fields and ophthalmoplegia. A syndrome produced by an aneurysm of the internal carotid artery includes loss of the sense of smell, ptosis of the eyelid, dilation of the pupil and ophthalmoplegia. Because of pressure on the cavernous sinus, there may be congestion of the vessels of the eye and swelling of the veins of the face. The fifth nerve may be involved with pain in the face. Noises in the ear and sometimes impaired hearing on the side of the aneurysm occur.

The absence of a bruit in most cerebral aneurysms or the absence of characteristic roentgenologic findings makes uncertain the recognition of the lesion as one caused by an aneurysm. The roentgenologic findings considered most characteristic are calcification in the wall of the aneurysm and unilateral enlargement of the optic foramen. Erosion of the carotid canal or unilateral erosion of the sella turcica is very suggestive of aneurysm. Arteriography, using a suitable opaque medium such as thorotrast, may allow visualization of an intracranial aneurysm in the carotid system.

Thoracic Aneurysm: The commonest symptoms of thoracic aneurysm are pain in the thorax, dyspnea, cough and hoarseness. The symptoms are characteristic of any mediastinal mass that produces pressure. The pain usually is unilateral rather than substernal and in the group reported by Mills and Horton, pain was confined to the left side of the thorax in more than two-thirds of the cases. In some, the pain may be situated only in the region of the shoulder and may extend to the arm. Pain in the back is rare. Maneuvers affecting intrathoracic pressure such as exercise, coughing and deep breathing may aggravate the pain. There may be true anginal pain as a result of involvement of the orifices of the coronary arteries by the underlying pathologic process. Dyspnea is a frequent symptom, whereas cough, hoarseness, palpitation, hemoptysis and dysphagia are less common than dyspnea.

The observation of a palpable mass which is not necessarily pulsating is the most characteristic finding. Tracheal tug and paralysis of the vocal cords occur in about a fifth of the cases. Mediastinal widening can be demonstrated by percussion in about half the cases. When the aneurysm is of considerable size such evidence of mediastinal pressure as venous congestion and cyanosis may be obvious. Audible cardiac murmurs are not characteristic but when they occur in the presence of syphilis one should suspect that an aneurysm is present. Roentgenologic examination of the thorax and especially roentgenoscopic examination are important aids in establishing the diagnosis of thoracic aneurysm.

Abdominal Aneurysm The symptoms of aneurysm of the abdominal aorta are merged compared with those of thoracic aneurysms because of the greater freedom of expansion in the abdominal cavity than in the cage of the thorax. In more than half of the cases reported by Mills and Horton symptoms directly referable to the aneurysm were not present. The first intimation of the condition may be a palpable pulsating mass first noticed by the patient or by a physician during routine examination of the abdomen. It is well to call attention to the fact that the normal abdominal aorta may pulsate unusually forcibly the so-called dynamic aorta and may simulate the pulsation of an aneurysm. Vague abdominal pain may be complained of and gastrointestinal symptoms such as nausea, cramps and diarrhea are occasionally noted.

The penetration of the blood stream through an atheromatous plaque with dissection of the middle coat forms a dissecting aneurysm. Dissecting aneurysms are commonest in the aorta and constitute a grave complication producing characteristic symptoms that are of great aid in diagnosing this condition. According to Glendy, Castleman and White one should suspect that a dissecting aneurysm is present when one or several conditions are encountered, namely: (1) Sudden onset of pain reaching its maximal intensity quickly. (2) tearing or crushing pain situated in the thorax but less often in the abdomen. (3) pain lasting for hours or several days which does not respond to usual measures for the relief of pain. (4) history of hypertension. (5) severe prostration. (6) slight or moderate fever and leukocytosis. (7) evidence of arterial occlusion. (8) unexplained anuria and (9) sudden death.

Aneurysm of the Peripheral Arteries The common symptoms of an aneurysm of a peripheral artery are a pulsating mass and symptoms and

signs of pressure on the nerve accompanying the artery. The results of pressure on nerves is especially noted in cases of popliteal aneurysm in which peroneal palsy often results if the aneurysm is not removed. The thrombus within the aneurysmal sac may interfere with the circulation to the extremity and results in ischemia, when complete occlusion occurs gangrene may result.

Treatment. An aneurysm of the extremities often may be excised successfully. The condition of the collateral circulation must be given careful consideration before excision is attempted. Unfortunately, aneurysms of the peripheral arteries are usually on an arteriosclerotic basis and the arteriosclerosis also affects the collateral arteries and reduces the potential collateral circulation. The collateral circulation can be estimated satisfactorily by employing the Moszkowicz Matrix test previously described in the section on "Treatment of Acquired Arteriovenous Fistula" (page 1679). If the thrombus has occluded the artery completely and if there is little evidence of ischemia of the distal portion of the extremity, the collateral circulation can be assumed to be adequate. Aneurysms of the peripheral arteries seldom rupture but they frequently produce pressure on an accompanying nerve which may result in paralysis. For this reason, it is justifiable to attempt excision of the aneurysm if the collateral circulation is reasonably adequate. It is not wise to wait too long for a collateral circulation to develop, for the possibility of paralysis occurring during the waiting period must be considered.

Methods of obliterating aneurysms of the aorta and of the larger arteries of the trunk by electrolysis and by insertion of foreign bodies are not very satisfactory. From the medical standpoint, a program and medication for reducing the blood pressure if hypertension is present, and the avoidance of overexertion may afford considerable protection to the patient. If syphilis is present proper treatment should be instituted and if congestive failure of the heart is present the usual relevant methods of treatment should be employed.

In certain cases of cerebral aneurysm, ligation of the homolateral carotid artery in the neck can be carried out successfully. It is well to remember that among young persons the carotid artery may be ligated without risk whereas among persons whose ages are greater than 35 years the risk of hemiplegia developing increases in proportion to the age. Before attempting ligation, it should be demonstrated that the patient

can withstand manual occlusion of the artery for as long as 30 minutes. The operation should be performed under local anesthesia and a trial ligature should be placed around the artery. If vertigo, faintness, weakness or numbness should occur, the ligature should be removed and permanent closure should be attempted at a later date if sufficient collateral circulation can be developed.

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CHAPTER LVIII

ARTERIOSCLEROSIS OBLITERANS

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ETIOLOGY¹

In spite of the fact that arteriosclerosis has been long recognized and studied we do not fully understand the *etiological* factors responsible for its development. This is in part due to the facts that arteriosclerosis develops slowly through the years, that laboratory animals are not entirely satisfactory for experimental production of this condition and that a certain degree of confusion still exists as to the exact diagnosis in many instances.

Following Marchand's² definition we consider arteriosclerosis to be a diseased condition of the artery wall with thickening of the inner layer, accumulation of lipid substances and degenerative changes after calcification and distortion of the arteries. The so-called Monckeberg sclerosis is closely related with calcification of the media in the muscular arteries of the periphery and hyaline transformation of the arterioles with lipid deposits. A questionable relationship to certain factors does apparently exist.

Age: In general there is in man a parallel incidence of increasing arteriosclerosis with increasing age. This is not, however, by any means constant. There are many instances of young persons 35 to 40 years old with marked evidence of sclerotic changes and in contrast many individuals 65 to 70 years old who even on post mortem examination reveal surprisingly few signs of sclerosis.

Certain changes do take place in the arteries with increasing age. Among these is the gradual diffuse distention due to progressive deterioration of the elastic tissue. This stretching process occurs in the longitudinal as well as a circular direction. From early youth there is a tendency to splitting of the internal elastic membrane which becomes more marked as the years progress. Arteries are under longitudinal

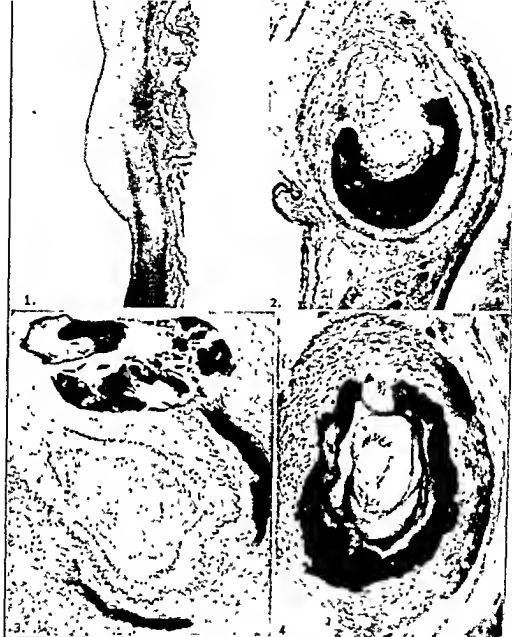


FIGURE 1 $\times 20$ Atherosclerosis obliterans. Atheroma of a peripheral artery. Marked by irregular thickening of the intima with very early degenerative changes in the deeper portion. The muscularis does not show significant changes.

FIGURE 2 $\times 170$ Atherosclerosis obliterans. Cross section of a peripheral artery showing thickening of the intima with almost complete obliteration of the lumen. This is due to proliferation of the endothelium and the connective tissue of the intermedial layer. Degeneration and calcification has taken place in the intermedial and muscularis layers forming a crescent. The elastic laminae are not clearly seen.

FIGURE 3 $\times 167$ Atherosclerosis obliterans. Cross section of a peripheral artery showing some thickening of the intima but this is not as marked as in Fig. 2. The laminae elasticae are here shown clearly being obliterated only where degeneration of a large area has taken place. The degenerative and calcific changes are in at present used in the most suggesting the so-called "Mönckeberg sclerosis."

FIGURE 4 $\times 170$ Atherosclerosis obliterans. A somewhat different type of involvement in which the intima and intermedial layers have been destroyed and replaced by calcification. The muscularis is relatively intact.

tension early in life but by the average age of 40 stretching has taken place relieving this tension and from then on overstretching occurs resulting in tortuosity. This deterioration of the elastic tissue with age is similar to processes which take place in all similar colloidal substances.



FIGURE 3. Arteriosclerosis obliterans. X-ray of leg and foot showing definite evidence of arteriosclerosis of both the posterior tibial and dorsal pedis arteries. This finding is of value in establishing the diagnosis but does not determine whether the vessels are patent or closed. For this other tests including palpation, oscillographic readings and sometimes arteriographic studies etc. are essential.

Another change associated with advancing age is the progressive accumulation of finely divided calcareous material in the media. This begins quite early in life becoming marked with the onset of senescence.

Winternitz and his coworkers³ have recently published studies which suggest that the changes above mentioned may be secondary to minute hemorrhages from the vasa vasorum. This will be discussed in detail later.

The fact that there is not an exact parallelism between age and the development of sclerosis inclines us to the belief that age *per se* is not

the cause of these changes but that they are secondary to one or to many of the factors which may enter into the life of the individual during the passage of time. The more significant of these possibilities will be discussed.



FIGURE 6. *Arteriosclerosis obliterans*. X-ray of foot showing definite evidence of arteriosclerosis of the posterior tibial artery with no change in the dorsalis pedis. This illustrates the manner in which arteriosclerosis may involve isolated segments of the arterial tree anywhere in the body.

Race and Climate: Studies of the effects of race and climate on the development of arteriosclerosis have thus far been unsatisfactory and inconclusive. Clinical observations have been incomplete by their very nature. The cause of death, as recorded, too frequently ignores the factor of arteriosclerosis and post-mortem records are not available in satisfactory form and detail for comparative studies on a large enough series of cases. Indirect observations have been attempted by analyzing the effect of these two factors on the blood pressure. If these studies were satisfactory they might give us some information regarding sclerosis, since it is estimated that about two thirds of all cases of well marked arteriosclerosis have hypertension,⁴ and that a rather larger proportion of hypertensives may die from causes in which arteriosclerosis plays a part.^{5, 6} Unfortunately, however, the blood pressure observations are not at all conclusive due to many factors of error including the following. There are great differences among various racial groups in the percentage of the population reaching

the ages most subject to arteriosclerosis. The records of causes of death are extremely inconsistent and inaccurate. There has only recently been worked out a standard method for recording the blood pressure so that readings taken by one set of observers have been only rarely comparable to



FIGURE 7. Arteriosclerous obliterans. Scattered plaques of calcification along the course of the femoral artery in the thigh. Although this on a plain film appears scattered the x-ray does not indicate the extent of intimal thickening nor the presence of thrombi which may produce occlusion of such a vessel at any time.

FIGURE 8. Arteriosclerous obliterans. An arteriogram has shown in which the femoral artery was obliterated in the mid thigh but collateral branches carry the blood around the obstruction and back into the femoral artery just above the popliteal space.

those taken by another group. Unless an exact statement of the method of observation is included, which is too rarely the case, such studies are of doubtful value. No attempt will be made to analyze all of the literature in this connection, as it has been ably done by Stocks. Further, more care-

fully controlled, studies should be directed to the determination of the effect of climatic changes on the development of arteriosclerosis to the variations between different races in the same location but not their own countries to the variations between different races living in their own countries and to the relation of social class and occupation



FIGURE 9 Arteriosclerosis obliterans. An arteriographic study illustrating a complication of arteriosclerosis obliterans namely. A false aneurysm in the popliteal space produced by a split $\frac{1}{4}$ inch long through a calcified plaque in the popliteal artery. This had been previously diagnosed as a tumor the arteriogram clarifying the diagnosis. The clot was removed the slit carefully repaired and reinforced and a previously condemned leg was restored to normal.

Nutrition There is no doubt that diet is of primary importance in the maintenance of health and the achievement of longevity. There are several ways in which nutrition may possibly influence the development of arteriosclerosis. (1) Quantitative deviation from the optimal diet that is over or undersupply of total food intake or any of the necessary constituents such as vitamins proteins fats minerals etc. (2) changes

of the ratio of one foodstuff to another in the diet (3) abnormal reactions in the diet to optimal nutritional intake such as may occur in metabolic dyscrasias gastrointestinal diseases and other pathological conditions. No evidence has been found that chronic over or undernutrition of a purely caloric nature has any influence on the development of arteriosclerosis in animals (Weiss and Minot²). Unbalanced diets of various types on the other hand have resulted in changes similar to arteriosclerosis in man. Rabbits fed on diets of meat⁷ eggs and milk⁸ dried powdered organs (liver adrenal thymus)⁹ or cholesterol¹⁰ develop an arteriosclerotic type of lesion.

Experimental studies dealing with inorganic substances have failed to demonstrate that disturbed inorganic salt metabolism is in any way a primary factor in the development of arteriosclerosis.

It has been repeatedly noted that hypervitaminosis D produces changes in the vascular system with the deposit of calcium plaques. These lesions are not however, characteristic of human arteriosclerosis. The lesions occur primarily in the media instead of the intima and the changes result in calcium deposits rather than lipid changes.¹¹ No evidence has been produced demonstrating a definite relationship between the excess or insufficiency of other vitamins and the development of arteriosclerosis. Adequate studies are lacking in this regard however. In man despite clinical impressions there exists no proof that overnutrition leads to arteriosclerosis. Remarkably soft arteries are frequently found in obese patients. Evidence is also lacking that undernutrition is ever directly responsible for arteriosclerosis. No increase in incidence has been reported among the peoples of Central Europe who suffered from marked malnutrition during the World War. The children of that era have not yet however reached the usual age for the onset of sclerosis and we must wait to see whether dietary deficiency in early childhood manifests itself in arteriosclerotic changes in early senescence.

While some physicians hold that an abnormal ratio of various food substances especially in the form of a high protein intake increases the incidence of arteriosclerosis conclusive evidence to substantiate this is lacking. Eskimos living on an animal tissue diet do not show an increased evidence of renal or vascular disease.¹² Many studies of various racial groups and dietary régimes fail to establish proof of a relationship to sclerosis. Of interest are the studies of Ruffer¹³ who performed

autopsies on over 800 Mohammedan pilgrims and found arteriosclerosis to be as common as in Europeans. This is significant in that these individuals never take alcohol.

Fat has been considered a potential cause of arteriosclerotic changes but this has not been established in man by controlled observations. The animal studies dealing with this problem have already been discussed. Joslin¹⁴ and others have felt that a factor in the premature development of arteriosclerosis in diabetes has been excessive fat in the diet, body tissues, and the blood. This is frequently elevated in diabetes but it should be appreciated that diabetes is a disease affecting the general metabolism and the rôles of the various factors have not been fully evaluated. In nephrosis and certain types of nephritis high cholesterol content of the blood is found associated with early development of arteriosclerosis. In these diseases as well as diabetes it seems probable that the factors at work may be endogenous rather than dietary. Careful observations must now be made over long periods of time of the effect of the high carbohydrate, low fat diabetic diets on the incidence and severity of arteriosclerosis in diabetes.

In addition to the above mentioned data dealing with Mohammedan pilgrims, there is much rather conclusive evidence that alcohol is not responsible for the development of arteriosclerosis.¹⁵ Pathological studies show no increased incidence in alcoholics as against nonalcoholics.¹⁶ In fact some workers believe that it may retard the development of sclerosis as it is a cholesterol solvent and hence tending to prevent it from precipitating.^{17, 18}

No conclusive evidence is available regarding the effects of variations in the inorganic substances including the salts on the development of arteriosclerosis despite the rather commonly held theory that an excessive intake of sodium chloride may favor the occurrence of arterial disease.

Arteriosclerosis may on the other hand interfere markedly with the normal nutrition of the body. Even with a normal intake of properly balanced foodstuffs these patients often lose weight, develop deficiency diseases, and the tissues may be seen to undergo marked atrophy. Since the intake may be adequate the explanation for this appears to be on the basis of faulty utilization. This interference may take place at the point of absorption, in intermediate metabolic distribution or storage point, or at the site of utilization, namely, the cell to be nourished.

This cell suffers no matter where the interference occurs. In order to compensate diets rich in proteins vitamins and fruit should be used.

The problems of dietary influence on longevity have not been satisfactorily studied and analyzed. The effects of diet must be observed throughout an entire generation or several generations before conclusions may be drawn. The span of life of certain lower animals can be affected by changes in diet¹⁹ and there is a strong probability that such is the case in man. Contrary to frequently expressed theories differences in life span on this basis may not be dependent on arteriosclerosis alone but other conditions such as lowered resistance to infections deficiency diseases etc. may play an even larger part. Sherman²⁰ states that the benefit of better feeding usually becomes fully apparent only when it is continued throughout a large part of the life cycle and often benefit is greater to the second generation than the first.

Perhaps when we know more about the foods tending to cause and to prevent arteriosclerosis we will be able to affect its incidence in man. For the present an attitude of scepticism appears justifiable until further studies are produced.

Infections Acute and Chronic The whole problem of the relation of infections to the development of arteriosclerosis can be summarized as follows. *In spite of exhaustive surveys and experimental work there is little evidence in favor of the idea that infections play an important part in the pathogenesis of arteriosclerosis.* Following typhoid fever there are frequently deposits of lipoids in streaks and patches in the intima.

In tuberculosis rheumatism arthritis streptococcus viridans infections and in glomerulonephritis there is no special tendency to the development of arteriosclerosis (MacCollum¹).

Heredity While much evidence has been advanced to show a marked hereditary tendency in the incidence of hypertension and thus by inference applied to arteriosclerosis (Williams¹) the direct evidence applying to sclerosis is less conclusive. It does appear however that in certain families the occurrence of the symptoms and pathology of peripheral arteriosclerosis occurs at a younger age group than in others.

One must consider however in any such group the average age of these families as compared with others the type of work they engage in the worry and strain of their lives their dietary habits and other factors

In other words, the total environment of these individuals as compared with any groups taken as controls.

Worry, Exercise, Hard Work: These factors have long been considered as possible contributing causes to the development of arteriosclerosis. It appears that there is an increasing incidence of arteriosclerotic manifestations, especially among the classes who, because of our civilization, have added responsibilities with great mental strain. One must be cautious about drawing such conclusions, however, since these classes are now in general subjected to diagnostic studies when indicated, thus improving the percentage of correct diagnoses. Formerly, this degree of diagnostic skill was not available.

It has been recognized for some years that the sclerotic plaques are most often found at the site of greatest strain of the artery, that is, where bends occur, where branches are attached, or where the artery is affixed to a nearby bone. We have seen marked localization of arteriosclerosis in the vessels of the feet of former athletes who have subjected the feet to severe stress and strain as, for example, lacrosse and hockey players, hurdlers and cross-country runners. This problem needs further, more complete, study.

Lead: Lead has been definitely considered as capable of producing arteriosclerotic changes in man. Examples of this syndrome in printers, painters, and plumbers are often cited. Recently, however, the question has been reopened and cannot be regarded as finally settled.

Manganese: Manganese has also been suspected in this regard. While perivascular infiltration has been reported, the changes are not characteristic of arteriosclerosis.

SIGNS AND SYMPTOMS OF ARTERIOSCLEROSIS OBLITERANS AS IT AFFECTS THE EXTREMITIES

Arteriosclerosis must be regarded as a generalized disease with essentially the same type of process potentially taking place in any or all of the arteries at one time. While our discussion will, for the most part, be confined to the effects of this process on the extremities, it must be pointed out that occlusion of any arteries in the body interferes with the nutrition of the supplied tissues and hence initiates signs and symptoms which should aid in making the correct, but often overlooked, diagnosis.

1 Atrophy of the skin and nails with poor growth and brittleness of the latter is often the first sign. This is frequently not noticed or incorrectly interpreted but when noted especially in persons over 40 years old should indicate the need for a vascular examination of the affected extremity. The atrophy of the skin is frequently accompanied by lack of sweating.

2 Atrophy of the muscles often accompanies this syndrome with marked loss in circumference of the extremity and total weight of the individual.

3 A common syndrome which develops early is the combination of pallor on elevation and rubor followed by cyanosis on dependency of the affected extremity.²¹ One of these signs may be present without the other but usually both can be observed to some degree. When present without infection they are significant of vascular impairment. It should be emphasized that the palpation of an active dorsalis pedis or posterior tibial artery is not enough to disprove this conclusion in a given instance since the occlusion may be peripheral to the point of palpation. The color depends on the blood contained in the minute vessels of the skin and subcutaneous vessels. With impaired circulation when the extremity is elevated the blood drains quickly into the deep veins and is not replaced rapidly enough because of the inadequate arterial supply. The result is gradually increasing pallor to the point where the flesh appears almost pale yellow in color. On dependency the blood stagnates in these vessels not being moved along because of the lack of arterial pulse pressure and other factors at first producing a rubor which slowly becomes cyanotic as the oxygen in the blood is utilized. If the temperature of the limb is low 10° C (50° F) the blood will not part with its oxygen the minute vessels are damaged somewhat and dilate and the skin becomes bright red in color even though the blood flow is small. Thus increased heat tends to increase cyanosis if the blood flow to a limb is arrested.

4 At the time that the observations for rubor are being made the venous filling time²² should be noted as follows. Following elevation of the feet above the heart level sufficiently long to produce collapse of the superficial veins the feet are quickly dropped to a dependent position. The length of time necessary for the veins of the feet to fill up becoming prominent is determined. Normally this should occur in ten seconds or less. Longer periods of time indicate impaired arterial or capillary

circulation roughly in proportion to the amount of delay. One warning should be given. The observer must be most careful to be certain that the filling takes place from *below upwards* (from the distal portion centrally) *not* from above downwards since the latter action may be the result of incompetent venous valves permitting back flow.

5 In our experience edema, rarely, if ever, occurs as a result of arteriosclerosis alone. This is logical since the fluid is not dammed back and the venous pressure tends to be decreased rather than increased. As a coincidental finding, however, it is common since in this age group we have a marked incidence of heart and kidney disease and of nutritional deficiencies all of which may be the explanation of edema as it occurs in these patients.

6 The patients frequently complain that the foot or hand is cold and that it is very difficult to warm it up. Actual studies of the surface temperature confirm this observation in these patients and also in many others who do not appear to be conscious of the lowered temperature which accompanies arterial occlusion unless the collateral vessels have taken over the burden of the circulation satisfactorily. The normal skin temperature in a room of average temperature 20 to 25° C. (68 to 74° F) should average from 29.5 to 33.90° C. (85 to 93° F.) but many extremities with advanced arteriosclerosis persistently maintain temperatures as low as the level of the room temperature.

7. Accompanying the sensation of coolness, numbness and "pins and needles" are often mentioned by the patient. Occasionally the feeling of formication is also noted.

8 The arteries may be found to be tortuous where they can be observed or palpated, *i. e.*, the temporal, radial, brachial arteries. On palpation they are firm and not easily compressible. Frequently they are hard either uniformly or in scattered areas where calcification has taken place. It is hardly necessary to say that when occluded no pulsation can be felt.

9 Fatigue and weakness are common presenting symptoms of sclerosis. The usual complaint being that after walking a certain distance (*e. g.* one to six blocks or upstairs) the muscles of the legs or feet become unusually fatigued. This symptom increases until it becomes the pain of intermittent claudication.

10 *By pain of intermittent claudication* we mean the ability of the patient to walk a limited distance at which point a cramplike pain in the muscles of his lower extremity forces him to come to a dead stop. Following a few minutes of rest the patient can then go on for about the same distance before similar symptoms once more force him to stop. This is perhaps the commonest syndrome which brings the arteriosclerotic patient to his doctor. The pain most commonly occurs in the muscles of the arches, calves or thighs and is characterized by a feeling of dull aching fatigue or a sense of cramplike constriction in the affected muscles. The severity of the claudication is frequently increased by cold weather. It is also made more severe by walking rapidly or uphill. As the disease progresses with blockage of the larger vessels the areas of claudication ascend the leg until the time when the thigh is involved and the vessels of that area are found to be occluded.

It should be noted, however, that in some patients the major trunks may be patent whereas some of the branches supplying important groups of muscles may be occluded. This must be differentiated at times from types of rheumatic or arthritic pain. In addition to tests for vascular or joint damage we have found it helpful to question the patient as to whether he has to sit down to get relief. The patient whose problem is *in the joint usually has to take the load off that joint to obtain relief* whereas the pain due to ischemia (true claudication) can be relieved by merely ceasing to actively exercise the muscles.

The explanation for this seems logical in the light of our present understanding of the cause of claudication pain. It is apparently the result of some chemical substance accumulated during muscular contraction when the blood supply is deficient. This syndrome can be readily reproduced by the application of a *tourniquet bound tightly enough around an extremity to occlude the arterial blood supply* following which exercise is undertaken. Roth²³ has shown that lactic acid of the venous blood of the affected extremity increases sharply after exercise in cases with occlusive vascular disease to essentially the same levels as in normal controls but this is not consistently parallel to the intensity of the pain. Whereas claudication pains in the calves usually indicate occlusion of the popliteal arteries we have seen a number of patients with this location of typical claudication pain and with the major vessels open down to and including the dorsalis pedis and posterior tibial arteries. We have explained

this as indicating involvement of branches supplying groups of calf muscles, and this has been demonstrated by arteriographic studies. This particular phenomenon has been noted more commonly in arteriosclerotic patients than in cases with thromboangitis obliterans but does occur frequently in the latter disease also.

11 Pains at night frequently occur in the calf and thigh muscles of arteriosclerotic patients. They are typically cramplike in nature and are believed to be due to a local ischemia which results from stagnation of the blood flow with secondary utilization of the oxygen and the accumulation of toxic waste products in the tissues.

12 Occasionally a patient is seen who has the most terrific rest pains in the feet with no demonstrable lesions aside from atrophy of the skin and muscles. We have seen examples of this so severe that despite all present-day methods of treatment amputation was required.

13 In general, however, the pain of arteriosclerosis is apt to be less acute, rather more of a dull, aching nature and it frequently accompanies the development of ulcers.

14 The ulcers of arteriosclerosis tend to occur about the toes, ankles or anterior tibia surface. They are usually dry rather than moist in nature, unless secondarily infected, which of course is rather common. They extend rather slowly, are often undermined on the edges and may develop a black eschar type of base. They may cause remarkably little acute, sharp pain, unless infected. These lesions commonly follow some trauma such as occurs in paring corns, or nails too closely or stubbing the toes. The damaged circulation will not properly care for even such a slight degree of trauma and an ulcer develops which may never heal. In a sense these ulcers represent the first stages of a gangrene, since they are perpetuated by inadequate blood supply to the area.

15 Gangrene in arteriosclerosis may be limited to a small area or massive depending on the size of the vessel involved and the completeness of its obliteration. The closure of major vessels such as the femoral arteries may take place, however, without the development of gangrene if the collateral arteries have taken over the burden of supplying the tissues to an adequate degree. When gangrene does develop it may begin as a small bluish spot commonly on one of the toes, gradually spreading eventually to involve the entire toe, foot or leg, at other times an entire toe may be involved at once due to occlusion of a supplying artery, or

if a major vessel occlusion suddenly occurs an entire limb may turn bluish black at one time. These gangrenous areas are frequently, though not always practically painless. They frequently progress to a dry mummified state unless infected. When mummified they tend toward self amputation. Frequently surgery is necessary to complete the severing process. Careful watch must be kept of the patient's general condition as the gangrenous areas spread. If evidences of toxicity begin to develop then amputation above the level of occlusion if possible should be done promptly. This is especially important in diabetic patients with arteriosclerotic gangrene. Methods for determining the correct levels will be described below.

The suddenness with which occlusion may occur in arteriosclerosis is not perhaps widely enough recognized. An artery may have sclerotic plaques along its walls for years without much interference with its function. Suddenly however a thrombus may form about a protruding portion of a plaque and occlusion may take place within a very short time. Many such episodes have been incorrectly diagnosed as embolic phenomenon. In the presence of auricular fibrillation the differential diagnosis may be very difficult. Fortunately the treatment which will be outlined below is essentially the same for the two conditions.

Findings by Means of Special Examinations. In addition to careful history taking and observation based on the above outline which will frequently be sufficient to establish the diagnosis there are additional tests which will help to confirm this impression and to establish the amount of damage involving the circulatory tree.

Oscillometric readings are very useful in determining the patency of major vessels and the level of their occlusion. After a study of many thousands of these readings we feel that there has been a tendency in some quarters to overinterpret and to draw unwarranted conclusions from such studies. It appears unwarranted to attempt a definition of the type of sclerosis involved but if we confine our interpretation to the level of occlusion which is what the machine actually determines valuable information can be obtained.

By increasing the air pressure in the cuff to the point where no pulsation is noted and then lowering it 10 mm. of Hg at a time recording the degrees of pulsation at each level it is possible to plot a curve. The shape of such curves has been the cause of much study but for practical purposes the important point is that of maximum pulsation and the

amount of pulsation at this point should be noted. When the major vessels are functioning pulsation will be noted. When they are not functioning no pulsation will be seen. This is much more reliable than palpation since such factors of error as pulsations of the examiner's fingers and aberrant locations of the vessels are eliminated. Furthermore, by moving the instrument up the calf or thigh the level of closure can be ascertained where palpation is obviously impossible. Readings should be made in a room where the patient is warm since chilling may produce spasm of the vessels and diminished pulsation. The average normal readings at various levels are as follows:

LEG		ARM	
Arch of foot	$\frac{1}{4}^{\circ}$ to $\frac{1}{2}^{\circ}$	Hand	$\frac{1}{2}^{\circ}$ to 2°
Above ankle	1° to 3°	Above wrist	1° to 3°
Below knee	2° to 5°	Above elbow	2° to 8°
Above knee	2° to 10°		

Oscillometric readings do not give us information about the collateral circulation which may take over the burden of the major vessels quite satisfactorily when the latter are occluded. This we must determine by other methods outlined below.

Surface Temperature Studies. It is often quite unnecessary to use a thermocouple to determine by the skin temperature that the circulation is impaired. While normal extremities may be either cool or warm, a marked difference between the two sides is very significant when they have been exposed to the same environmental stimuli for the preceding hour or more. This difference even when only a fraction of a degree centigrade can be readily recognized by the examiner's hands. The dorsal surface of the examiner's fingers is especially sensitive for this test. In arteriosclerosis the cooler extremity has the most markedly impaired circulation. If one wishes to record the difference and actual levels, a thermocouple or radiant heat measuring instrument should be used. The readings should always be interpreted taking into consideration the room temperature and no readings should be considered as indicative until repeated readings taken in a given environment fail to show fluctuations of more than 1° C.

Reflex Vasodilation Tests. Numerous tests have been described to produce reflex vasodilation and hence in a sense measure the potential arterial blood supply available at a given time. They are based on the

observation that if one part of the body is markedly warmed vasodilation will take place in other parts especially of the extremities. If this is done in normals the temperature of the part being tested can be elevated to 37.9 to 38.9°C (91 to 93°F). If the circulation to a given extremity is impaired markedly there may be no rise above room temperature. All degrees of impairment may be noted between these extremes.

Landis and Gibbons suggested immersing the uninvolved pair of extremities in hot water 43.3 to 44.3°C (110 to 112°F) for 20 to 40 minutes. Maddock suggested wrapping the patient in blankets and hot water bottles. The use of a heat pad on the abdomen or wrapping both arms in a heat pad is satisfactory. Other methods such as blocking of the properly selected nerves (e.g. posterior tibial for the feet) spinal and general anesthesia etc. have been used but are usually unnecessary except as a check on the simple methods in doubtful cases.

X rays—Flat Plates especially by means of a soft tissue technique are useful for determining the presence or absence of arteriosclerotic plaques along the course of the vessels under suspicion. They have in the past however been the source of great errors in interpretation. We cannot tell by the degree of sclerosis noted whether there is occlusion of the vessel or not. Vessels showing the most characteristic pipe stem calcification have proven on autopsy to be patent throughout and conversely vessels showing only a few scattered plaques have been occluded high up in the limb if the plaques located there happened to produce a thrombus at that level. This point is not sufficiently well appreciated by the medical profession as yet.

Arteriography Perhaps the greatest amount of information regarding the state of patency of the collateral as well as the main trunk arteries can be obtained by the use of a radiopaque substance directly injected into the arteries and x-rayed while in these vessels. The substance most widely used for this purpose is thorotrast (thorium dioxide sol.). It has the theoretical objection of being radioactive and being stored in the reticuloendothelial system where its radioactivity may be dangerous. For arteriograms only from 10 to 20 cc. of this substance is used and we have knowledge of thousands of such injections with complications of a minor nature only and much rarer than with transfusions or the use of arsenicals. Large series of cases have been followed after the injection of

75 cc for hepato or splenophotography. Yater has reported this to be an innocuous procedure even in these doses.

The technic requires close cooperation between the operator and the roentgenologist. Certain operators cut down on the artery (brachial or femoral) to insert the needle but we have not found this necessary, merely locating the artery by palpation and inserting the needle therein. This is occasionally difficult especially in obese patients. A size 16 to 18 gauge needle is used and after about 8 to 10 cc of the thorotrast has been injected the x-ray operator begins to take pictures. The extremity having been placed properly before the procedure was started. Serial plates will show the opaque substance in the main trunks, collateral vessels, arterials, venules and veins. Points of blockage and collateral repair are clearly seen. Effects of treatment can be followed by a recheck months later. It should be noted that the point of apparent blockage may in fact be a point of spasm which extends up the vessel walls well above the level of the organic occlusion. We have seen this released down to the latter level in the legs following a spinal anesthesia. No evidence of serious leakage of the arteries has ever occurred in our experience.

This must be classed as a useful procedure especially where detailed studies are being made and where proper facilities and well trained workers are available. It is not necessary for routine study in most cases of arteriosclerosis.

Numerous other substances have been used such as skiodan and uroselectan but thorotrast is less painful, less apt to produce a slough and generally more satisfactory than any so far advocated.

Histamine Flare Tests Histamine flare tests have been advocated as a test of the circulation. Following the injection of histamine intradermally a flare normally develops extending 1 to 2 cm from the site of injection. If the circulation is impaired this flare does not develop satisfactorily. It appears to us to be a test depending on the superficial rather than the deep circulation and the factor of the state of the lymphatic vessels seems to play a part. If a series of injections are made up a leg a rough idea of the level of impaired circulation may be gained by observation of the reactions. Perlow²⁴ feels that the temperature to which the wheal rises is more important than its size—normal wheals reaching a temperature of 33.6 to 34.6° C (92.5 to 94.5° F) for the upper extremities, 30° C (86° F) for the feet.

Measured Work Tests: If a patient is made to walk a certain distance or up a flight of stairs at a fixed pace and observed for the onset of claudication pains and the point beyond which he cannot proceed, valuable information will be gained for comparison with future studies after treatment.

Similar observations, perhaps, more accurate, can be gained by the use of various types of ergometers in which the patient lifts a weight by means of a walking motion such as we use, or where the patient is forced to contract his muscles by Faradic electrical stimulation (Landis and his coworkers) until the muscle can no longer function.

PATHOLOGY AND PATHOGENESIS

While arteriosclerosis is sometimes present in the relatively young, and while occasionally a person may reach the seventh decade with few or no observable sclerotic changes, it is, of course, common knowledge that the curve of incidence and degree runs roughly parallel to that of increasing age.

What then are the actual changes which take place in the arteries with increasing age? As has been stated the most striking change is that of distention due to the progressive deterioration of the elastic tissues.²⁵ This is especially found in the larger arteries and takes place in a longitudinal as well as a circular direction, thus accounting for the tortuosity so commonly observed. During an individual's lifetime there is also an accumulation of calcareous material in the media. From early youth there is a tendency to splitting of the internal elastic membrane which becomes more complete with increasing age. A fibrosis of the media is commonly observed with age but there is some question as to whether this is purely physiological. As this progresses a tendency to calcification is seen. The question as to the relationship of the fatty streaks so commonly seen in the aorta of young individuals to the development of arteriosclerosis is at present being debated and is unsettled.

Microscopically the cells of the intima in these areas are swollen, edematous, and loaded with fine anisotropic lipoid droplets consisting largely of cholesterol fat. This fat may be deposited in either the sub-endothelial layer, the musculoelastic layer or both. Possible causative factors are: (a) Cholesterolemia; (b) infectious diseases; (c) mechanical influences; (d) the inherent condition of the wall of the affected blood vessels.

In studying the pathology of arteriosclerosis a considerable variety of lesions is found which appear to be stages of development of the same process. The atheromatous type of plaques seen in the aorta wall may be found in other large arteries and develop as small round grayish or yellowish spots which begin to project on the inner surface of the blood vessel. These gradually fuse into irregular, large plaques projecting further into the lumen. The development of fibrous tissue makes many of these become milky white, while the fatty parts break down, becoming mushy. From this point either of two processes may take place. The lesion is sealed by the formation of a calcareous plate or the softening material breaks down, producing ragged ulcerative defects at the bottom of which there may remain necrotic material. Thrombi may then form and cover these ulcers.

Similar lesions in the arteries of the extremities do not usually contain as much lipid material. Muscular arteries show much more extensive involvement of the media. This probably explains the dilation and longitudinal stretching as well as the development of aneurysms. While the large arteries become dilated the smaller ones tend to become narrowed by atheromatous plaques and completely occluded by thrombosis. The arteries to different organs show variations in the manner of development of arteriosclerosis. Our interest in this discussion must be focused on the vessels of the extremities. As explained above there is successive splitting of the intima which in senility results in a marked thickening of this layer because of the secondary development of fibrous tissue. This thickening is irregular, resulting in the lumen becoming eccentrically located. Degeneration and necrosis involves the intima and media with the deposit of cholesterol crystals. Fibrosis involves the media and adventitia. The arteries then become calcified by the development of circular solid deposits of calcareous material at the more or less obliterated dividing line between intima and media, the "pipestem" effect. The final closure is usually due to thrombosis. The process in diabetic cases is essentially similar.

Mönckeberg's Sclerosis: In the arteries of the extremities a different type of arteriosclerotic process is sometimes found (Mönckeberg, 1903).

In this we find primary necrosis and calcification of the media which is not necessarily associated with intimal lesions. This is entirely different from atheroma in location and microscopic picture. The arteries are

converted into solid tubes. The deposits may be platelike, circular or tubular. This type of sclerosis occurs more frequently in the lower extremities than the upper. Monckeberg thought that it was a different process than the atheromatous type but they occur so frequently together that it is probable that they represent different manifestations of essentially the same phenomenon.

Recent Studies. The above descriptions represent in outline the older generally accepted concepts of the production of arteriosclerosis. More recently Winternitz³ and his coworkers have introduced evidence to show that arteriosclerotic processes may originate and progress in a somewhat different manner. It is of course entirely possible that we will find that several types of mechanisms may be capable of initiating these processes.

In the studies of Winternitz *et al.* especial emphasis has been laid on the importance of the mural vascular channels, the vasa vasorum, in this picture. It was noted that very frequently small hemorrhages, fresh and old, were found in the walls of the vessels associated with arteriosclerotic changes, that they frequently proximated the orifices of smaller arterial branches as is the case with sclerotic changes, and that in certain instances small vessels were associated with these hemorrhagic areas. Careful dissection and study has demonstrated fine networks of blood-filled capillaries on the intimal surfaces of the vessels, especially in the region of sclerotic plaques. It has previously been demonstrated that vasa vasorum are present in the adventitia and the outer half of the media. Careful clearing methods reveal the relationship of these vessels, hemorrhages and calcified plaques to be such that it appears that hemorrhage from these small vessels eventually may result in the arteriosclerotic plaques of arteriosclerosis. *Mural vascular channels have been found to be the site of pathological processes in arteries including:* (1) Occlusion by thrombus, (2) stasis of blood with lath formation, (3) obstruction and closure by overgrowth of the surrounding connective tissue, (4) and degeneration and necrosis in association with similar involvement of the tissues of the vessel wall.

Why thrombi form readily in some instances of damage affecting the intima of certain vessels and not elsewhere where the damage is greater is as yet an unsolved problem. There may be a relationship to the coagulating elements of the blood or to certain coagulating factors associ-

ated with local cellular changes. The organization of the thrombus within a vessel is characterized by the disintegration and digestion of the blood elements accompanied by growth into the clot of capillaries and fibroblasts together with many mononuclear phagocytes. This process extends until dilated sinusoids connected with tenuous narrow branches canalize the clot which in turn calcifies in other areas. This may result in rather bizarre formations of vascular channels incorporated as part of the main lumen of the vessel involved. These channels are at least frequently primarily extensions of the *vas vasorum* of the vessel wall. Thrombus formation may be initiated at times by exudative processes.

It is of interest that relatively few of the vessels of the *vas vasorum* have been demonstrated in the arteries of young individuals.

Numerous precipitating factors for these minute hemorrhages may be mentioned: dietary deficiencies especially of vitamin C, hemorrhagic diathesis of various types, increased capillary fragility of other types including *chemical poisoning*, *parasitic infection* and other causes.

These authors conclude that while hemorrhage and perhaps lesser excitations are not the only source of the materials that form atheroma, they are potent contributing factors. Certainly the hemorrhagic necrosis of intimal tissue already laden with fat-filled cells results in the most extensive coalescence of lipoid materials in which cholesterol crystals and the debris of cells are found—calcification of the lesions of the artery wall is not a process which differs from calcification elsewhere. The primary requisite necrotic tissue preferably rich in lipoids is found in abundance in the vessel wall.

Leary²² has already challenged these studies as being inconclusive.

While the evaluation of this approach must rest with further study and time, it should at least greatly stimulate interest in arteriosclerosis as a biological phenomenon other than purely degenerative in nature.

True and False Aneurysms in the Peripheral Arteries. The purely dilated saccular and dissecting aneurysms are rather commonly noted and recognized as occurring in arteriosclerosis. False aneurysms are in our experience less correctly diagnosed. They may occur at any point but usually where stress and strain is common as at the peripheral space. The sclerotic artery actually splits or erodes through a plaque with a resulting hemorrhage into the surrounding intracellular space. A clot quickly forms which picks in firmly forming walls which may be in re-

than as much in thickness and made up of all of the elements of an old thrombus

Arteriolar changes may be the dominant factor in the picture and may be histologically divided into three main types ²⁶ (1) *Intimal hyalinization* which is the arteriolar counterpart of simple arteriosclerosis more widespread and severe with advancing age (2) *Medial hypertrophy and degeneration* which resembles changes following distention of any hollow muscular structure. The medial degeneration may be primary in some instances but the medial hypertrophy is probably secondary to stress and strain being present more frequently in hypertensives than in non-hypertensives (3) *Intimal proliferation* which in the form of endothelial hyperplasia with increase in elastic tissue and secondary degenerative changes is classified as endarteritis obliterans rather than arteriolar sclerosis

TREATMENT

The attitude of hopelessness with which the treatment of arteriosclerosis obliterans was formerly regarded is slowly changing to one of a constructive active approach based on scientific and empirical observations of recent years. The result of this change has been a reduction in the number of amputations, the healing of arteriosclerotic ulcers and the reduction of disability and pain.

The following procedures are of sufficient importance to warrant discussion.

1 **Rest** Rest of the part is of general importance with the following qualifications. Any extremity with an ulceration or early gangrene should be relieved of any stress or strain. For example such a foot should not be used in standing or walking. When sclerosis is present without serious trophic changes or ulceration the extremity may usually be exercised up to the point of pain. It is inadvisable for the patient to force the part beyond that point since it indicates the accumulation of toxic products and tends toward gangrene with the further accumulation of these substances.

2 **Position** The position in which the limb is placed is of considerable importance for if elevated too much the tissues may become ischemic whereas if it is lowered too far they become engorged with cyanotic blood which may also interfere with proper tissue metabolism. In general if the limb is lowered until the tip is about six inches below the heart level

that will be found to be a satisfactory position. If the limb is elevated and then lowered slowly to the level where the superficial veins just fill this will be found to be about six inches below the heart level and the correct position.

3 **Exercise.** Complete rest may, by its very inactivity, result in gradual stagnation, improper tissue nutrition and cramplike muscle pains. For this reason carefully controlled exercises have been described and used to encourage the collateral circulation to take over the burden of supplying the tissues. Perhaps the best known are those described by Buerger²¹ which consist in principle of the patient lying flat in bed elevating the legs for two minutes, lowering the leg over the edge of the bed for one minute and resting it on the bed for two to three minutes. The timing should be varied so that the color changes of pallor on elevation and rubor on dependency are observed, and yet not maintained for more than a few minutes.

Allen²⁸ has described certain helpful foot exercises as follows. The legs are hung over the edge of the bed and the feet are exercised by flexing and extending the ankles, turning the feet inwards and outwards, spreading and closing the toes. These should not be done in the presence of gangrene.

Exercises of these types should be performed two or three times daily for as long as possible (up to 20 minutes) without undue fatigue or claudication pain. An improved color and an increased warmth commonly result.

4 **Tobacco.** It has now been generally recognized that the use of tobacco in the presence of impaired circulation is inadvisable. It was first noticed by Silbert²⁹ and others that in thromboangitis obliterans smoking was a marked aggravating, if not indeed the commonest etiological factor. Most clinics subscribe to this theory, at least in reference to aggravation. Experimental studies by Maddock and Collier,³⁰ Barker,³¹ Wright and Moffat³² and Lampson³³ established the fact that the smoking of tobacco usually produces diminution of the blood supply to an extremity, normal or otherwise, by constriction of the peripheral arteries, as determined by thermocouple readings, capillary microscopy and plethysmographic studies.

An attempt by Harkavy and his coworkers³⁴ to place the effect of tobacco in thromboangitis obliterans on an allergic basis has been opened

to serious question by the work of Trasoff Blumstein and Marks³⁵ and Wescott and Wright³⁶

Thus far, the only established mechanism involved is the physiological one of constriction of the small arteries and arterioles. For the arterio-sclerotic patient with already impaired circulation this is sufficient to interdict its use. While spasm of the sclerotic vessels is not considered important, one must remember that the life of the tissues frequently depends on collateral vessels that these are usually not sclerotic and that they may be constricted by smoking. If for example the circulation in an extremity is already impaired to a fraction of its former potential to let us say, the point where life of the tissue is in doubt then the deciding factor is the production of gangrene. This principle operates in all degrees and in our mind indicates that patients with definitely impaired circulation from arteriosclerosis or any other cause should completely abstain from the use of tobacco.

5 Alcohol. In contrast the action of alcohol is definitely vasodilating in its effects on the peripheral arteries. In experiments performed in our laboratory,³⁷ rises in temperature of the tips of the extremities following the injection of 60 to 90 cc (2 to 3 ounces) of whiskey have been as great as 5 to 6.7° C (9 to 12° F) depending of course on the condition of the vessels and the control level preceding the experiments. We therefore feel that the use of whiskey or other spirituous liquors is indicated in the treatment of organic occlusive peripheral vascular disease. Among the most important indications is that of arteriosclerosis. There is general agreement in this among most of the leading vascular clinics today. The dosage depends on the severity of the condition. With impending or actual gangrene the patient should receive enough to keep the peripheral vessels as dilated as possible. Often the patient will be kept very slightly inebriated during the critical period. This may require 30 to 60 cc (1 to 2 ounces) every four hours or more frequently. This may be tapered down as the emergency subsides to 30 to 60 cc (1 to 2 ounces) once or twice a day, which is the dosage usually recommended in nonacute cases. As Brown and Allen pointed out in addition to the vasodilatory properties, whiskey may control the pain in some cases of peripheral vascular disease more satisfactorily than morphine.

Unless there are definite contraindications such as severe diabetes gastric ulcer or alcoholism we feel that these patients should have some alcoholic beverage each day the remainder of their lives

6 Baths The proper use of baths constitutes a definite contribution to the treatment of arteriosclerosis These may be grouped under several headings as follows

(a) *Contrast Baths* Perhaps the most generally used type of bath for this condition is the contrast bath Two containers are placed side by side They should be deep reaching to the knees In one water of the temperature 40.0°C (104°F) is placed In the other water of the temperature 13.3° to 20.1°C (56 to 70°F) (tap water temp) The legs are placed first in one and then the other alternating at short intervals of one to three minutes The last immersion should always be in the hot water We have suggested seven alternations beginning and ending in hot water This should be done once or twice a day depending on the condition of the extremity The theory is that the patient vessels are exercised by producing alternating vasoconstriction and vasodilation There are however several objections to this type of bath which has resulted in our abandoning its use Firstly the best containers only reach the knees The blockage may be far above that level so that while the contrast baths may produce different metabolic demands the ability to respond may not be realized at the level of the stimulus Secondly when vessels already damaged are forced into sudden vasospasm they may remain closed complicating the picture considerably Thirdly in our experience there is often severe pain during the cold phase perhaps due to cramping or marked ischemia We have therefore adopted the long used Sitz bath for this purpose

(b) *Sitz Baths* With the technic used we have the patient sit in a tub containing at least 12 inches of water at a temperature 37.8° to 40.2°C (100°F) for a period of 20 to 30 minutes at least once a day This overcomes all of the objections raised above in reference to the contrast baths The heat extends high enough for collateral arteries from the trunk and femoral arteries to be activated No cold water being involved the risks of sudden permanent occlusion or even severe pain are minimized If water of this temperature appears to cause discomfort the temperature may be reduced to 34.4 to 36.7°C (94 to 98°F)

(c) *Whirlpool Baths* Whirlpool baths if available may further stimulate the circulation the motion of the water being helpful especially in the presence of a chronic low grade ulceration. The temperature of the water should be about the same as with the Sitz baths.

(d) *Soaks* Wet dressings have largely been abandoned in our clinic because of their tendency to get cool even under the most favorable conditions. This produces vasoconstriction and thus does more harm than good by defeating our chief aim that of improving the circulation to the dying cells. In their place for ulcerated or gangrenous extremities we use soaks of boric acid solution or normal saline with the temperature 35.7 to 37.8°C (96 to 100°F). These may be repeated two or three times daily for from 15 to 30 minutes. After each soak the foot is removed dried carefully and placed under a warm lamp cradle thus preventing chilling. The object should be to allow proper drainage by softening and clearing away crusts which tend to lock in infection but once infection is under control attempts should be steadily made to produce a dry lesion rather than a wet macerated one. Healing is made more rapid and danger of infection is reduced in this condition when the lesion is dry.

(e) *Heat* The problem of heat is one of great importance in the handling of arteriosclerosis obliterans. It is probable that in the past heat has done far greater harm than good because of its improper use. Properly used it will attempt to reproduce normal temperature conditions. The normal surface temperature rarely exceeds 33.9 to 35°C (93 to 95°F). In order to achieve this and hence stimulate normal metabolic processes the temperature of the surrounding environment should approximate that level we therefore use thermostatically controlled heat cradles which keep the temperature between 30.4 to 35.7°C (90° to 96°F). * By careful watching and the use of a thermometer an equal distance from the lamp to that of the extremity it is possible to use ordinary light bulbs but the factor of error is great and no doubt many of these cases have been greatly aggravated by such overheating in the past. As Starr has pointed out³⁸ increasing the metabolic demands beyond the capacity of the supplying arteries points to increasing gangrene. Temperature controlled heat within these limits is in our opinion the only safe form of heat for use in this condition. The general

* We have found those made by Valvede Laboratories New York City satisfactory.

use of heat lamps diathermy or short wave machines is to be condemned. The author has seen over 50 cases of severe ulceration or gangrene which appeared to be precipitated by these measures—seven patients lost their legs and two died—not as a result of their arteriosclerosis but rather of the results of this misapplied treatment. This we have emphasized previously.³⁹

Tissue Extract It has been determined during the past few years that extracts may be prepared from many tissues of the body which possess vasodilating properties. Some of these probably depend largely on their content of choline compounds and histamine for their effects but others appear to retain their effectiveness even after the removal of these substances. Credit for much of the original work in this field must go to Frey and Kraut⁴⁰ Wolffe⁴¹ and Barker and Roth.⁴² In our clinic studies have been carried on for the past five years with the use of pancreatic tissue extract No. 568 (Sharp & Dohme) a heart muscle extract (prepared through the courtesy of Eli Lilly & Co.) another pancreatic tissue extract (Grant Co.) and recently an active principle isolated from No. 568—depropanex—(Sharp & Dohme). Although these substances are capable of varying degrees of immediate vasodilation and epinephrine antagonism many workers feel that the more lasting effects produced may be due to some additional factors.

Animal studies have demonstrated the vasodilating and epinephrine antagonistic properties. In man two effects have been established. These have been measured by studies of individuals suffering from typical arteriosclerotic intermittent claudication. Firstly there is a definite increase in muscular work capacity as measured by delayed onset of claudication pains within one half to two hours following the injection of one dose of the extract intramuscularly. Secondly there is a gradual improvement in the capacity for work following a considerable series of repeated injections. This is the basis for the therapeutic use of these substances. In our experience the chief usefulness of such material is in the treatment of typical intermittent claudication. Numerous refinements in the original tissue Extract No. 568 have in our opinion made the present product—deprotienized pancreatic tissue extract (depropanex) the most satisfactory preparation thus far subjected to clinical trial. When given two to three times weekly in the form of intramuscular injections increasing from 1 to 3 or 4 cc. over a protracted period

of time it increases the walking distance of about 60 per cent of these patients markedly. This is really valuable since only a few years ago intermittent claudication was regarded as a hopeless progressive condition. We have a large number of patients formerly able to walk from $1\frac{1}{2}$ to 2 blocks who can now walk from $1\frac{1}{2}$ to $1\frac{3}{4}$ miles. Others have not improved to such a degree but are now able to carry on work for which they were formerly barred by their inability to get around. Improvement should not be expected in the average case with fewer than 20 injections. Tobacco is interdicted especially during its use since nicotine is an active antagonist to the desired action.

We have conducted controlled experiments with injections of inert solutions without similar effects. At our suggestion the Sharp & Dohme Laboratories fractionated the original extract No. 568 in an effort to isolate an active principle. Depropanex (deproteinized tissue extract) has been one of the results. Although this appears at present to be the most satisfactory of these preparations further work may produce others more effective.

Pressure Suction Boot Treatment. Although variations in the environmental pressure have been used in the treatment of impaired circulation since before 1700 it remained for Landis and Gibbon⁴³ and Hermann⁴⁴ to perfect suitable mechanical apparatus and to popularize this principle for widespread use in the treatment of peripheral vascular diseases.

The principle on which the modern apparatus is established depends on the hypothesis that blood flow in an extremity can be increased markedly by exposing that extremity to fluctuations in pressure from positive to negative and back to positive continuing such alterations for the duration of the treatment which may be from 1 to 24 hours or more. The extremity is contained in a so-called boot made of glass or metal in which the pressure changes are produced by means of connections to a correctly constructed air pump system. The opening through which the leg is inserted is made airtight by means of any of a number of types of rubber cuffs. There have been certain disagreements as to the type and timing of the cycle to be used and the amounts of pressure and suction desirable—it presents the most commonly used cycles approximate those suggested by Hermann and are as follows—accepting the base line as atmospheric pressure (760)—one complete cycle takes 15 seconds of which

the first three seconds are positive pressure reaching gradually 90 mm of Hg. There is then a gradually downward curve crossing the base line in the third second and proceeding to a negative pressure of -80 mm of mercury at the eleventh second. A more rapid return to the base line completes the cycle in 1½ seconds. This is repeated continuously for the duration of each treatment. Certain objections had to be met to make this treatment satisfactory theoretically and practically. In order to operate the boot the cuff around the upper part of the extremity must of necessity be airtight. This produced a certain degree of constriction about the limb and hence interfered with the blood flow—especially of the superficial vessels. Many types of cuff have been devised and some have at least partially overcome this objection.

In general when the circulation to an extremity is increased there is an increase in the surface temperature of that extremity. It was noted in our clinic and elsewhere that the temperature of the limb was often colder following this type of treatment than before. This may have been due to the constriction above mentioned or cooling due to the continuous flow of air in and out of the boot. As a result of that observation local or reflex heat has been used with improvement in this regard. By reflex heat we mean the application of heat over other areas of the body, e. g. a heat pad over the abdomen which produces a secondary reflex vasodilation of blood vessels of the entire surface including the limb in question. Here of course the degree of dilatation depends on the potential capacity of the vessels damaged and undamaged. As in all new or rediscovered methods of treatment the first claims represented a somewhat optimistic picture of the usefulness of the method. It was stated that it was of great value in arteriosclerosis senescent and diabetic thromboangiitis obliterans, Raynaud's disease, acute embolism, frostbite and other forms of circulatory impairment. *Actual experience with this apparatus has in our opinion greatly narrowed its indications. At present we find it useful in only a few cases of uncomplicated senescent or diabetic arteriosclerotic gangrene, cases of acute embolism or thrombosis and frostbite.* Even in certain of these cases we must confess we are not absolutely convinced as to its value. On the other hand certain contraindications for its use have been definitely established.

Pressure suction should never be used in the presence of acute or subacute infectious processes, any form of acute or subacute thrombo

phlebitis (which excludes most cases of thromboangiitis obliterans) or any case in which evidence of autolysis of the tissues is noted as in cases of acute embolism, or thrombosis (e g., arteriosclerotic sudden occlusion) in which after several days the skin begins to become mottled and blistered. In these groups the results may be serious following its use.

The Use of the Sanders' Oscillating Bed: A form of mechanized treatment which has recently been used in a number of clinics is the motor bed described by Sanders⁴⁵ By means of this 'so-called' oscillating bed the head and feet of the patient are alternately elevated and lowered, a complete cycle taking from 1 to 2½ minutes The movement is smooth, the patient soon becomes accustomed to it and we have had patients on these beds for as long as two years. The beds have been in operation day and night except at times when the bed was being shipped, as the patient moved about the country. The degree of the tilting and the speed of the cycle can be regulated within reasonable limits The object is to exercise the arteries which are still able to function by producing rubor and pallor (engorgement and ischemia) in a manner similar to the Buerger's exercises but continuously and without fatigue to the patient. This process is gentle, involves no constricting bands and appears to be theoretically sound, especially in the treatment of arteriosclerosis with or without gangrene. We usually use a thermostatically controlled cradle at a temperature of 35.7° C (96° F) as an adjunct treatment While the total experience with this equipment has been rather limited, we have now had the opportunity to study about 100 cases Clinical impressions are often deceiving guides and experimental studies are not available, but so far the workers in our clinic and in other clinics have been very favorably impressed Healing of ulcers has taken place in certain patients after complete failure of the pressure suction boot and many patients can use this equipment who were made very uncomfortable by the action of the boot. Thus far the indications for its use appear to be advanced arteriosclerosis of the vessels of the legs with impending or actual early gangrene The results in certain of these cases have been encouraging in that the progress of the symptoms of the condition has been stopped and reversed with marked improvement and healing. We should like to suggest a thorough study of its possibilities in cerebral arteriosclerosis for which to date there has been no treatment of sufficient value to be taken seriously.

Progress in this type of case is slow and we find it usually necessary to keep the patient on the bed for at least one month. In our experience treatments of a few hours duration are not satisfactory. We have set as a minimum in our clinic eight hours a day.

Intermittent Venous Hyperemia This phenomenon proposed as a form of treatment by Collens and Wilensky⁴⁶ is based on the work of Lewis and Grant⁴⁹ who demonstrated that following occlusion of the blood flow for a considerable period of time (15 to 20 minutes), when the flow was released it not only returned to normal but actually produced a hyperemia sometimes increasing the blood flow as much as 600 per cent above normal. The apparatus devised by Collens and Wilensky produces a state of venous stasis and release in periods of about two minutes each by means of a blood pressure type cuff around the limb which is alternately inflated and deflated by means of a motorized pump. The degree of inflation can be controlled 30 to 80 mm. of Hg pressure usually being used. These workers have reported very favorable results in the treatment of arteriosclerotic claudication and gangrene and of thromboangitis obliterans. Workers in Scotland have reported similar results. Although we used an apparatus of this type for over one year in an attempt to establish its usefulness we finally gave it up being unable to convince ourselves of its value. Allen and his coworkers of the Mayo Clinic reported disappointing results.⁴⁷ Workers at Mt. Sinai Hospital using phthysmographic studies and Veal using oxygen saturation studies are both about to report unfavorably upon the actual physiological response resulting from this form of therapy. At present therefore while not denying the possibilities of this theory of treatment we feel that its widespread use is not to be recommended pending further study of varying cycles and pressures.

Saline and Other Solutions Intravenously Following the use of normal and hypertonic saline and citrate solutions for thromboangitis obliterans by Koga,⁴⁸ Meyer,⁵⁰ Ginsberg,⁵¹ Silbert⁵² and others certain workers have adopted this form of therapy for the treatment of arteriosclerosis obliterans. There are no satisfactory theoretical grounds for this and the therapeutic effects claimed do not in our opinion warrant acceptance pending the presentation of more adequate scientific data. If used empirically the usual dose is 300 cc. of three to five per cent saline solution intravenously. Five per cent is more potentially dangerous so

that the lesser concentration is preferred. The treatment should be given twice or three times a week. As stated above while its use in thromboangitis obliterans is at least debatable its use in arteriosclerosis seems to us to be unwarranted.

Vasodilating Drugs Numerous drugs have been used in the treatment of arteriosclerosis obliterans on the basis of their vasodilating powers. The commonest of these may roughly be divided into

- (a) The nitrites and allied compounds
- (b) The theobromides, theocalcines and allied compounds
- (c) The choline compounds
- (d) And papaverine

After years of study both clinical and experimental with all of these groups I believe that it is fair to state that their value singly or collectively in the treatment of arteriosclerosis obliterans is very limited.

Briefly the action of the nitrites is too fleeting and the dilation as it affects the vessels of the extremities is only observed with difficulty.

The action of theobromine and its allied compounds in the usual dosage is very unreliable and doubtful.⁵³

The action of certain of the choline compounds while of established value in certain diseases of the peripheral circulation appears to be of no value in the treatment of arteriosclerosis.⁵⁴

Papaverine has been advocated for the relief of sudden occlusion and its general vasodilating qualities.^{55, 56, 57} In a recent study we have found its vasodilator effects to be highly unreliable and not nearly so marked as the effect of simple reflex heat.⁵⁸ The relaxing effect of this and other opiates and the value of this relaxation is undoubted. They should be used wisely and with the possibility of ultimate habituation in mind although it has not proven to be a serious factor in our experience. A combination of papaverine, pantopon and strinal (spasmalgin) has proven to be especially helpful when used intravenously for acute pain. Morphine should only be used as a last resort because of the familiar objections of nausea, distention, habituation, etc.

The long standing use of potassium iodide in the treatment of arteriosclerosis merits its mention here although clinically we have been unconvinced of its actual value. Animal work does seem to demonstrate that it will prevent the actual laying down of cholesterol plaque and it has been given empirically clinically for many years.

The Use of Antiseptics in Arteriosclerosis In all cases involving impaired circulation the use of strong antiseptics is to be condemned. It should be remembered that the antiseptic will not serve its intended purpose if in addition to destroying invading organisms it also destroys the very delicate tissue cells which are attempting to establish a healing process. We do not advocate therefore the use of iodine the mercurial antiseptics the silver salts the phenols or any other similar preparations. Hot soaks in boric acid solution or normal saline as previously described are much to be preferred. We have found some stimulating substances such as the chlorines (dilute) (azochloramid solution 1:1000 in tricein) and balsam of Peru to be helpful. For clearing away old slough and purulent sinuses benzine has frequently been very satisfactory when other solutions have failed to help. The primary object in most instances should be to improve circulation and to stimulate the regrowth of tissue rather than to produce a temporarily sterile wound around which the tissues are dead.

Surgical Aspects of Arteriosclerosis While it is not within the scope of this work to present in detail the technics involved in such surgical procedures as may seem necessary in arteriosclerosis certain principles of established importance will be outlined.

The use of wet dressings hot soaks and antiseptics have been discussed previously. To reemphasize (1) Wet dressings should not be used unless they are kept warm—temperature $34\frac{1}{2}$ to 37.8° C (94 to 100° F). Chilling should be avoided and the tissues should not be permitted to become macerated and boggy. In general unless infection is present the gangrenous areas should be kept in a dried condition. (2) Hot soaks are usually preferable to wet dressings. They should be at the above mentioned temperature and should be given once or twice a day for 30 to 60 minutes. (3) No strong antiseptics should be used since the life of the epithelizing cells is the most important single factor in the majority of these cases.

Ganglionectomies and other operations designed to produce vaso dilation are in our experience of no value in the treatment of arteriosclerosis obliterans since spasm is not an important factor even when as is rarely the case present. The same may be said for *periarterial sympathectomy* since the major vessels being organically occluded cannot dilate to any effective degree.

Peripheral sympathectomy by either crushing, alcohol injection or section of the mixed nerves supplying the feet may be helpful for the relief of pain. For the correct technic the reader is referred to Smithwick and White⁵⁹ or Laskey and Silbert.⁶⁰ This is rarely necessary and should not be used in the upper extremities since the motor fibers are destroyed at the same time as the sensory fibers and while this is not so vitally important when it involves small intrinsic muscles of the foot it is very serious when it involves the hand muscles. Unless severed there is usually a regrowth of the nerve fibers in from four to six months. The procedure should be performed with the greatest care to avoid trauma to the tissues, since healing is sometimes difficult because of the impaired circulation which may be a factor high above the level of the gangrene. It is necessary to know thoroughly the location of and the tissues supplied by each nerve in order to accomplish the desired results. Even then in our experience the presence of aberrant branches or nerve fibers may result in unsatisfactory results, the pain being inadequately relieved.

Amputation: The selected site of amputation is vitally important for successful healing. The day of amputating slightly above the level of the gangrene, whether it be in the toe or the foot, just because the skin looks good there, is over. Too often the tissues under that innocent appearing skin are sorely undernourished and the skin itself too poorly supplied with blood to permit healing. This approach leads to repeated amputation with a marked increase in mortality and prolonged invalidism.

We do not amputate today until nature has done her best to demarcate the area involved, to localize any infection present and to attempt self amputation. If self-amputation has progressed sufficiently in a toe some times a moderate amount of help by the surgeon will complete the job and lead to local healing. If infection fails to localize, the gangrene continues to spread, or there is a systemic reaction taking place as a result of septic absorption, amputation is the only recourse but not until a thorough study is made to determine a level at which healing can be reasonably expected. For this we use modern methods instead of guesswork. *The oscillometer will tell us where the major vessels are occluded and in the absence of further data it is unsafe to operate below that level.* The use of arteriographic studies using thorotrast (thorium dioxide sol.) gives us great information regarding blockage of the major vessels and

the extension of the collaterals. At times we are encouraged to amputate lower than the level of major blockage if very extensive collateral circulation is seen to be present. The histamine flare test is helpful in studying the circulation in the skin. If this reaction is inadequate the skin will in all probability fail to heal. Using these technics we are able to conserve the maximum amount of limb possible; we are able to reduce the number of reamputations markedly and as a result reduce the mortality appreciably. This represents an intelligent conservative approach to the problem of amputation which at best always represents an admission of defeat—our inability to save the extremity for future usefulness.

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CHAPTER LIX

RAYNAUD'S SYNDROME AND ACROCYANOSIS

By IRVING S. WRIGHT, M.D.

RAYNAUD'S SYNDROME

Definition: Raynaud's¹ original descriptions of a syndrome producing symmetrical gangrene included case reports of several different diseases according to our present understanding. There is still a considerable degree of confusion in the minds of many physicians regarding the types of cases which should or should not be included in this category. A recent review of the subject² resulted in the substantiation of certain primary requirements for diagnosis as follows: (1) Gangrene or trophic changes limited in a large degree to the skin. (2) Symmetrical or bilateral involvement. (3) Absence of evidence of occlusive lesions of the arteries. (4) Intermittent attacks of changes in color of various local areas which usually precede the trophic changes by months or years. Additional secondary criteria are also of some value in this connection and will be discussed later.

PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Major pathological findings in Raynaud's disease are conspicuous by their relative infrequency. The early manifestations of the disease seem to be on a vasomotor basis without established demonstrable pathology in the nervous system. This statement is made after consideration of certain claims of pathological changes in the sympathetic ganglia and in the spinal cord. These claims have not yet been confirmed. Later, changes may occur in the local small arteries with a tendency towards occlusion. This appears to be secondary to the repeated episodes of constriction. Vessels larger than the digital vessels do not tend to become occluded. Examination of the capillaries of the nailfold reveals a characteristic picture in late cases. These vessels become markedly dilated, especially the venous limb of the loop. The dilation gradually tends to extend including the arterial limb. The explanation for this dilation may rest in the repeated erythematous phases following the spastic phenomenon

during which time the loops are filled with blood to the point of overstretching.

The gangrene is usually superficial and localized to small areas, such as the tips of the fingers or toes, nose, ears, cheeks, chin, etc.

It has been the subject of some debate as to whether this gangrene is due to a local circulatory fault or to a purely vasomotor phenomenon frequently repeated and of sufficient severity to produce anoxemia of the tissues to the point of local death. We believe that both factors play a part, that the original attacks are due to the vasomotor phenomenon, and that these gradually produce damage to the local arteries, followed by ischemia and death of the cells. This only occurs in severe cases. Many individuals have a Raynaud's vasomotor phenomenon intermittently for years without progression to gangrene. This we classify as a pre-Raynaud's syndrome since it is not possible to predict which of these cases will show progression to the gangrenous stage.

Observation of the nailfold capillaries during the cycle of the attack presents a good picture of the local pathological physiology involved. In the first phase, that of waxy pallor, few capillaries are visible, filling of the loops is incomplete and they have a segmented, broken appearance due to the fact that the walls are invisible and the column of blood cells is interrupted and static. No blood is entering the capillaries from the arterioles which are in spasm. The surface temperature of the involved areas is low usually approximating room temperature. In certain instances intermittent leakage may occur from the arterioles and by retrograde flow from the venules. If this occurs the capillaries may become more easily visible, in fact even distended. This blood is relatively static also and as deoxygenation takes place the part assumes a cyanotic hue. There may be patches of cyanosis and rubor during this phase. With the cessation of the attack the arterioles open up, pouring blood rapidly in the capillaries and vessels which become markedly dilated with red oxygenated blood. Some areas may remain cyanotic for a time since the supplying arterioles may not open simultaneously in all areas. The surface temperature of the erythematous areas rises rapidly to above the average 30.5 to 33.9° C. (86 to 93° F.) during this stage.

Since scleroderma of the affected parts is so common a complication of the Raynaud's syndrome, a discussion of the pathology of this condition must be included.



Raynaud's syndrome showing extreme pallor and moderate cyanosis associated with the vasospasm produced by exposure to cold

In the involved areas the skin becomes tightly stretched, and the malpighian layer is atrophied. The deeper layers become fibrosed. Histologic examination shows hypertrophy of the collagen and stratum granulosum.^{4, 5} This fibrosis extends into the subcutaneous layers, the muscles and may bind the skin to bones which lie relatively near the surface.

Arteries such as the digital vessels are surrounded by fibrous tissues.⁶ Their channels are narrowed by intimal thickening and the external pressure resulting from the fibrosis. Pigmentation of the skin occurs at this time. Marked bony changes of several varieties may take place. Arterial changes may be of either atrophic or hypertrophic type. These changes combined with the fibrotic changes of the soft tissues not uncommonly result in ankylosis of the joint usually in a somewhat flexed position. Atrophy of the digital terminal phalanges is a common finding. This begins at the tip and gradually destroys the entire phalanx.

It should be noted that this process may involve the entire surface of the body and also the internal organs such as the larynx, lungs, kidneys and bladder. The most commonly infected areas in our experience are the fingers (sclerodactylia) hands, arms, toes, nose, cheeks and ears. The more marked the involvement the lower the skin temperature. In advanced cases it approximates the environmental temperature level.

Examination of the capillaries in this condition shows them to be scattered, seen with difficulty, and constricted with an occasional dilated one to be found.⁷ Stretching of a finger obliterates them with paling of the skin. Relaxation of the finger brings more into action as the pressure is released.

ETIOLOGY

The fundamental etiological factor in the production of the Raynaud's syndrome in the sense of a specific agent is not known. It is not even known whether it is on a bacterial, allergic, hormonal, or on some entirely different basis.

We do, however, know that certain stimuli are capable of initiating individual attacks. The most important of these factors is probably:

1. Cold: If an individual with this syndrome is exposed to cold to a sufficient degree spasm of the affected areas takes place and this is not relieved until the environmental conditions are changed with an increase in the temperature level. Different patients respond quite differently to this stimulus. With some the temperature level must be quite

low t_e , 4.5 to 7.3° C (40 to 45° F.), with others who are more sensitive to cold the attack can be precipitated by a drop to much higher levels, t_e , 18.3 to 21.1° C (65 to 70° F.). This is not infrequently seen during swimming with the water at that temperature. Chilling of the body usually induces spasm of the affected areas at higher levels of temperature than if the body is kept warm. In the other hand, as Lewis has pointed out, cold stimulation applied to the base of a finger may produce a typical attack of vasospasm limited to that area.

The result of this reaction to cold is that the symptoms are usually much more pronounced in winter than in summer months, and in the north than in the south. Certain advanced, highly sensitized cases continue to have their spasms under remarkably warm climatic conditions.

It should be noted that exposure to extremely cold (4.1 to 2.9° C, -25 to 30° F) water may fail to produce the spasm. If the skin is sufficiently cold the blood will not give up its oxygen, the minute vessels are damaged, become dilated, and the skin becomes bright red.

2. **Emotion:** A second factor of great importance in the production of attacks is emotion. Anger, fear, and excitement may all be capable of producing attacks in certain individuals. In some patients these factors may accentuate the effects of cold, in others the attacks may be produced by emotional stimuli alone in a warm room.

3. **Repeated Vibration or Percussion Stimuli:** Relatively recently attention has been drawn to the fact that certain individuals who use vibrating tools such as pneumatic drills, rivet hammers, etc., may develop a traumatic, vasospastic phenomenon comparable to the Raynaud's syndrome. The reaction may take place during the action of the machine especially in a cool environment or the individual may apparently be sensitized to cold by this repeated trauma. The cases thus far reported have been for the most part in individuals using the type of equipment above mentioned. We are at present engaged in preparing case reports in patients who have developed similar syndromes following repeated slight trauma of a variety of types. In this group are included a typist, a concert pianist, a telephone operator, a handball coach and others. The pianist was forced to give up his work for three years since each time he started to play the spasm occurred. The telephone operator developed the syndrome in one hand, the hand she used in "plugging in," in which procedure she frequently pinched her fingers between the plug



Beginning erythema ten minutes after return to warm environment.

and the switchboard. Superficial gangrene developed and she changed hands using the good hand. Within a few months this hand became similarly involved. These patients continue to have trouble if they continue their occupation unless they receive proper treatment which will be discussed later.

4 **Occlusive Arterial Disease** It should be recognized that in the early stages of occlusive arterial disease, e g., thromboangitis obliterans, arteriosclerosis, etc., the Raynaud's syndrome may occur. This is probably due to the fact that with the lumina of the vessels narrowed and the walls damaged they are especially susceptible to irritation such as cold and slight spasm becomes a factor.

5 **Arsenic** It has been suggested that this syndrome may develop as a result of the ingestion of arsenic either intentionally as in medication or unintentionally as on fruit skins.⁸ A check in our clinic of the presence of high arsenical urinary figures failed to produce any conclusive figures proving such a relationship. One might expect a high incidence of Raynaud's phenomena among treated luetic patients but this has not been noted.

6 **Disturbed calcium metabolism** has been claimed as the important factor⁹ in the production of this syndrome but in our opinion the evidence so far presented is too inconclusive to prove this point.

7 **Sex Hormones** The possible relationship to certain sex hormones should be mentioned. The Mayo Clinic has repeatedly published figures showing a sexual incidence of 95 per cent in females. This would appear to carry possible significance. In our clinic however the incidence in males appears to run nearer to 30 per cent thus giving the female ratio of 70 per cent. *These may still be significant figures and work on the potential importance of sex needs further study.*

SIGNS, SYMPTOMS AND COURSE

From the viewpoint of the clinician it is helpful to recognize four stages of the Raynaud's syndrome. The reason for this is that any case may develop the signs and symptoms of any of these stages and may then either progress, remain in *status quo*, or tend toward improvement.

1 **Pre Raynaud's Syndrome (Early Raynaud's Syndrome)** In this classification fall the mildest cases, many of which do not progress, merely showing a spastic response to cold throughout the patient's life span with

no demonstrable pathology ever developing. Others do show progression, but so far as we know it is impossible at present to predict without consecutive observation which cases are benign and which seriously progressive. Certain patients have fewer symptoms after middle life.

A typical attack may be described as follows; the hands will be described as the affected part in this hypothetical case, other parts, if affected, react similarly.

Following exposure to stimulation, *e. g.*, cold, emotional upset, etc., the fingers begin to blanch turning a grayish color due to the deoxygenation of the remaining blood. The minute vessels frequently go into spasm forcing the blood out and producing a waxy color. If they remain patent filled with static blood, the spasm being confined to the arterials, the fingers become increasingly cyanotic. Cyanosis may also be produced by intermittent leakage from either the arterials or venules as explained under *pathological physiology*. If the finger is cut during this period no bleeding will occur from the waxy flesh and only slight oozing from the cyanotic areas, since both of these changes are manifestations of lack of blood flow. As these changes take place gradually increasing numbness is felt by the patient. In extreme cold this may progress to an aching type of pain but in our experience severe pain is rare at this stage. This phase usually remains as long as there is no change in stimulation, *e. g.*, so long as exposure to the requisite low temperature continues. These areas are especially susceptible to frostbite at this time.

With the removal of the stimulation, *e. g.*, cold, anger, the second phase, that of rubor begins. The affected area turns intensely red beginning at the proximal portion. This intense redness spreads like a wave distally completely enveloping the cyanotic or pale area. Some sections may remain patchy with alternating rubor and cyanosis for a brief time until all of the spastic vessels open. As this transformation takes place sensations of "pins and needles," tingling and even burning may be complained of. The finger temperature may become abnormally high, the vessels are overdilated. This phase may last a variable length of time, usually about 20 minutes, after which the fingers return gradually to their normal appearance, temperature and feeling. The cycles may occur repeatedly on stimulation, sometimes many a day, at other times at much longer intervals. In general it appears that the more severe and more frequent the attacks the more apt the condition is to progress, but the

exceptions to this rule are numerous enough to impress us with the probability that these are not the most important factors

2 Trophic Changes Among the first evidences of progress of this condition are early trophic changes at the tips of the fingers toes nose or ears. These trophic areas are characterized by small dents and scales of brownish dry skin occasionally but not always preceded by tiny ulcers. The ulcers may be very painful in proportion to their size but the trophic areas are not in themselves painful. If the condition progresses further larger ulcers involving the entire surface of the tip of the digit may occur. These are apt to be excruciatingly painful and are frequently moist and somewhat punched out. Most of them are however relatively superficial. As a result of these trophic changes and ulcerations the tips of the digits may be deformed and shortened.

3 Scleroderma (Sclerodactylia, Acrosclerosis) It should be made clear that there are cases of scleroderma which do not appear to be related to Raynaud's syndrome in any way. Perhaps we are not justified in including scleroderma as a stage of progression in the Raynaud syndrome. Yet there is a very high incidence of patients with this syndrome who develop sclerodactylia (scleroderma beginning in the finger tips) adding greatly to the seriousness of the symptomatology and complicating the therapeutic approach. The skin becomes increasingly hard tense shiny and pigmented. As explained under the heading of pathology the fibrosis responsible for this may become fixed to the bones and joints and produce a fibrotic ankylosis although the joint may not actually be involved at first. Later hypertrophic and atrophic changes may be noted. The skin loses its natural color the capillaries become increasingly difficult to see often resembling shadows without definite structure. The typical attacks of Raynaud's syndrome are more easily produced. Frequently the stage of rubor does not occur because of the pressure and tension of the skin and subcutaneous tissues.

The sclerodermatous changes may involve any portion of the extremities trunk or face including internal organs. Pain is rarely a major factor if uncomplicated—stiffness and tightness being more commonly complained of. If however ulceration occurs there is often excruciating pain and tenderness. In addition a syndrome known as calcinosis may further complicate the picture. Deposits of calcium may occur under any portion of the body surface not infrequently at the elbow knee

ankle or digital joints. If this calcified substance works its way out to the skin it usually produces considerable discomfort. At times it is necessary to remove some of this calcified material surgically to relieve the pain. It tends to recur at the same areas. The fingers gradually become fixed in a slightly flexed position. In advanced cases the hands may become useless.

When the face is involved the expression may be changed due to the tightness about the nose and mouth obliterating all wrinkles and making facial movement difficult. The neck may be stiffened. Numerous spider angiomas may appear, especially about the face. Whether actually a part of Raynaud's syndrome or not the two conditions occur so frequently with parallel courses in the same individual that one cannot adequately discuss one without considering the mutual relationship. Treatment for Raynaud's syndrome is quite different when scleroderma is present. This will be discussed later.

4. **Gangrene:** Frank, massive, gangrene involving large portions of fingers, toes or other areas is, as we see this syndrome today, a rare complication. It was reported more frequently in the older literature but careful analysis of these descriptions forces one to conclude that certain of those cases were, in reality, cases of thromboangiitis obliterans, others ergot poisoning, or frostbite, which may occur rather easily in patients with the Raynaud's syndrome while the vessels are in a state of spasm. If spasm of the arterial tree does occur with sufficient severity and frequency organic occlusion as a result of clotting or changes in the vessel wall may take place. This as stated above is in our experience rather rare in uncomplicated cases today.

TREATMENT

1. **Protection:** In the pre-Raynaud's and mild cases of Raynaud's syndrome the treatment should be largely protective. The first step should be to avoid repeated producing stimuli, *e. g.*, exposure to cold, extreme emotional crises, etc. If trauma is the precipitating cause the vocation or avocation should be discontinued or attacks will continue to occur.

The best way to protect patients from the cold is to have them remain in a warm dry climate during at least the winter months. If other factors play the major rôle, however, this will not control the syndrome.

If southern winters are not possible, every effort must be made to avoid extreme exposure. Winter sports, such as skating and skiing, are potentially harbingers of frostbites for these patients and should be avoided. The same holds for out of door winter work. When it is necessary for the patient to be out in cold weather, warm body clothing, warm socks, muffs, and gloves should be used. Shoes should be large enough for one or even two pairs of woolen socks without crowding. Small chemical heaters are valuable for use in the pockets or muffs to keep the hands warm. Electric heaters are of value in driving automobiles.

2. Treatment of Local Conditions: It is important not to suddenly overheat an area in spasm since unfortunate burns may occur before the circulation is adequate to carry off the excess heat and to handle the suddenly increased metabolic demands. Warming should be undertaken slowly.

Strong antiseptics such as the iodines, mercurials, silver salts, etc., should be avoided since they may do more harm to the epithelization of an ulcer than to the bacteria present. Infection is rarely the important factor in these cases and mild antiseptics such as boric acid, normal saline, and azochloramide in triacetin 1:500 solution should be used if necessary. These ulcers heal best when dry. Hot soaks (temperature 36.7 to 37.8° C.—98 to 100° F.) using normal saline are recommended for one hour each day when infection is present. If wet dressings are used care must be exercised to keep them warm since chilling will tend to produce spasm of the vessels, preventing healing.

3. Mecholyl Iontophoresis: Iontophoresis using acetyl b methyl choline chloride (mecholyl) was first recommended from the Vascular Clinic of the New York Post Graduate Medical School and Hospital^{10, 11} for the treatment of various circulatory disturbances. Its use in the treatment of Raynaud's syndrome and scleroderma was suggested and later reported upon in detail by Duryee and Wright¹². In summary we have found, after five years of experience involving about 75 patients with this syndrome and several thousand treatments, that:

(a) Mecholyl iontophoresis is a palliative treatment for patients suffering from uncomplicated Raynaud's syndrome—decreasing the severity and frequency of the attacks in the mild cases and healing the ulcers in the more severe cases. It is not a cure and does not prevent attacks under severe provocative conditions, *e. g.*, extreme cold. We have found

it useful in helping these patients through the winter months when they are forced to stay in the northern climate

(b) Mecholyl iontophoresis appears to be the most effective treatment thus far suggested for scleroderma. After persistent frequent treatments about 70 per cent of our patients have shown definite treatment of varying degrees. Some have been remarkably improved as in the case of the Italian woman who had been bedridden unable to even feed herself because of stiffness of her fingers for seven years and who after 75 treatments was able to get about and after 165 treatments does her own housework including washing and ironing. As in most stubborn conditions all patients do not respond equally well and about 30 per cent have been disappointing. This group was for the most part advanced with evidence of involvement of the internal organs or infection such as bronchiectasis which certain of these cases develop. Severe nervous shock has caused a relapse in several patients. A number of these patients had previously undergone unsuccessful surgery including ganglionectomies and parathyroidectomies. Details concerning the first 34 cases may be found in the paper dealing with this problem.¹²

Technic. The details of the treatment may be found in Kovacs¹¹ report. Briefly they are as follows:

(a) Necessary equipment

- 1 Galvanic machine with a smooth current
- 2 Malleable electrodes and connecting wires
- 3 An electrode pad 10 to 12 square inches
- 4 Bandages
- 5 Asbestos paper or cloth
- 6 Solution of mecholyl 0.25 per cent

(b) *The special asbestos paper or cloth is dipped in the solution and applied over a severely involved area—such as the hands or arms. No holes through this must be left open.*

(c) The malleable electrodes are wrapped about this area and fixed in place by the bandages making sure that nowhere does the metal come in contact with the skin.

(d) These electrodes are connected to the positive pole of the galvanic machine.

(e) The negative electrode pad is moistened in water and placed elsewhere on the body surface usually in the middle of the back and connected with the negative pad.

(f) The current is very gradually turned on and increased to 15 to 20 milliamperes—kept at this level for from 30 to 10 minutes and gradually turned off

(g) If the patient complains of a burning sensation the treatment is discontinued immediately and the electrodes readjusted

Treatments are given at varying intervals from daily to biweekly depending on the severity of the case. Frequent treatments produce better results rarely is improvement seen under 20 to 30 treatments.

The exact mechanism by which this improvement takes place is not understood. The drug is absorbed into the skin and produces increased local circulation. The capillaries become more visible. The skin gradually becomes softer and more pliable. Ulcers formerly unhealable become healed. It appears to be largely a local phenomenon but sclerodermatous areas in other parts of the body are also improved. This does not represent a completely satisfactory form of treatment for this stubborn disease but seems to be the most encouraging therapy either medical or surgical which we observed in over 70 cases studied. For that reason it is worthy of a serious trial in each instance.

4 *Vasodilating Drugs—Nitrites Papaverine* The vasodilating drugs of this type do not appear to affect the course of either the Raynaud's or sclerodermatous syndrome. They may produce a relaxation of spasm but usually not if the producing factor is severe and still present. A mixture of nitrite compounds has been suggested for use prior to going out into the cold to prevent a spasm; this mixture includes rapidly and slowly acting nitrite (vasodilator compound B. W. & Co.). Further studies must be made to determine its real value. Papaverine hydrochloride is of questionable value¹¹—warm water being more effectual as a reflex vasodilator.

5 *Tobacco* The use of tobacco by patients suffering from the Raynaud's syndrome may be soundly contraindicated on the basis of its vasoconstricting tendencies and the probability that the more frequently constriction occurs in the small vessels the more apt permanent damage is to result. On the other hand smoking does not appear to have the specific severe aggravating effects in the Raynaud's syndrome that it does in thromboangitis obliterans. Until further studies clarify this problem we advocate that all moderate and severe cases stop smoking. Thermocouple tests may determine which patients are particularly susceptible.

6. **Surgery of Raynaud's Disease:** It is the purpose of this presentation to discuss only the general aspects of surgery for Raynaud's syndrome and scleroderma and the results of the various methods used. Our conclusions will be based on the experience of our own and other active vascular clinics. Certain statements may be made with relative conclusiveness at this time.

(a) No conclusions may be drawn as to the clinical result in any patient until that patient has been followed for at least one year after the operation. The literature has been full of reports of little value in which cases have been reported on a basis of one to six months post-operative follow-up. There is frequently a nonspecific improvement with encouraging surface temperature studies and lessened symptomatology for a few months. The results at the end of one year in the same patient may be entirely negative.

(b) Lumbar ganglionectomies are simpler technically and hence more satisfactory in general than cervical ganglionectomies. Unsatisfactory results are usually due to the fact that all of the necessary fibers have not been cut.

(c) In general the more advanced the condition the less satisfactory the results.

(d) Ganglionectomy rarely benefits scleroderma and in advanced cases is valueless.⁶

(e) Parathyroidectomy has been recommended for scleroderma⁶ but in the few cases we have seen after one year there has been slight or no improvement. Several of these have reported a temporary improvement lasting for from three to six months.

(f) The only surgery holding forth a reasonable chance of success, ganglionectomy or parathyroidectomy, is major surgery which should be attempted only by men who have special training in the field, and even then should not be entered into lightly from the viewpoint of the patient.

With these facts in mind it may be stated that in uncomplicated but progressively severe cases of the Raynaud's syndrome properly performed ganglionectomy offers a very good chance of relief from attacks and the comfort of warm extremities. Whatever the fundamental pathological physiological process may be it is probably not affected by this procedure but the nerve impulses producing the attacks are blocked and the disagreeable symptoms and sequelae are held under control.

We do not recommend it in early cases since many of these do not progress as stated above. If they do show evidence of progression however with increasingly severe symptoms it is wise not to wait too long until the disease has reached an advanced stage with sclerodermatous changes if good results are to be achieved. Since the condition progresses slowly there is usually a period of several years during which its course may be studied—only in the very rare fulminating case is it necessary to make a hasty decision in this matter.

For details as to the preferred surgical technique for the treatment of this condition the reader is referred to the excellent summaries of White¹⁴ Adson and Brown¹ and Craig and Horton.¹⁰ The relative merits of the different methods of approach are discussed in these presentations.

It appears to us that further carefully controlled surgical studies may produce a more satisfactory approach to the understanding and treatment of this syndrome.

ACROCYANOSIS

There has been a tendency on the part of certain workers¹⁴ to classify acrocyanosis loosely with Raynaud's syndrome. While these syndromes have certain points in common such as blueness of the extremities and response to cold there are many points of difference such as lack of the characteristic Raynaud attacks, presence of marked sweating and the presence of edema in acrocyanosis, the difference in sex distribution and other factors. In our opinion therefore precise objective thought is hindered by attempting to group these two conditions under the same general heading. Rather then differences should be more completely studied.

SIGNS AND SYMPTOMS

The word acrocyanosis was first used by Crocq¹ to describe a syndrome in which the hands and feet become a deep blue especially in a cool environment. The blueness gradually fades out at the wrists and ankles respectively. The volar surfaces are moist—freely sweating—the dorsal surfaces are dry. Pressure produces a white spot which slowly disappears. As pointed out by Stern¹⁸ this description requires amplification in several aspects as follows—the cyanosis is not permanent as Crocq originally thought but disappears in all but the most extreme cases when

the environment is sufficiently warm. Secondly, edema is often seen in extreme cases.

When normal human skin is cooled it turns a light blue in color due to contraction of the arterioles and small arteries with resultant stasis and deoxygenation of the blood in the capillaries and subcapillary venous plexus. Acrocyanosis represents an extreme phase of this reaction, the blue being a much deeper shade than in the normal.

The color of the cyanosed skin is frequently not uniform, there usually being scattered red areas (so-called marmar red spots). The depth of color is generally greater in the dependent position. The white spot noted by Crocq to be caused by local pressure disappears spontaneously in a characteristic way,¹⁸ the color returning in from about a second to one minute from the periphery only rather than from below also as in normal skin. Local edema is in our experience fairly common. It may produce merely a sensation of tightness or in extreme instances may even reach the stage where pitting is possible. This is not seen in the Raynaud's syndrome.

Gangrene and ulceration do not occur in acrocyanosis except where frostbite or some other factor enters the picture. This is in contrast to Raynaud's syndrome. When lesions traumatic or otherwise do occur, however, they tend to become septic and heal with difficulty. Another feature of interest is the remarkably slight disability noted in even advanced cases.

Occasionally the follicles of the skin become abnormally prominent. The sweating of the palms and soles of the feet offers a marked contrast to the Raynaud's syndrome. We have seen patients from whose hands sweat would drop regularly and very frequently, that is, one to five drops per minute. This occurs in a cool environment in which gross sweating would ordinarily be absent. Kuno¹⁹ has shown that perspiration at low temperatures occurs more on the palms and soles than elsewhere, is increased by hyperemia and failing to evaporate collects on the surface. This really represents the condition of acrocyanosis. When the circulation to the skin is shut off perspiration becomes minimal and the skin becomes dry as in the Raynaud's phenomenon.

Increased sweating keeps the stratum corneum moist and pliable. In patients who do little manual labor the layer tends to atrophy and the

amount of perspiration being greater than necessary keeps the skin wet. In day laborers by contrast we find extremely thick horny dry skin.

Kuno has also shown that mental stress will cause sweating of the palms and soles. In cool environment this produces chilling of the part and in susceptible individuals tends toward acrocyanosis. In certain cases cyanosis of the face and other parts may be seen. Livido Reticularis is not an unusual accompaniment.

In general the symptoms and signs are much more marked in winter than in summer. Even in extreme cases the normally palpable arteries are always patent the circulatory interference being due to spasm of smaller vessels.

ETIOLOGY

While many etiological theories have been suggested only six factors thus far considered seem worthy of discussion.

1 **Cold** Cold seems to be the one universal precipitating factor producing attacks in susceptible individuals—whereas heat relieves them. While cold may well be considered the most important external factor it cannot be the sole cause or the disease would be more universal in persons exposed to sufficiently low temperatures.

2 **Mental Disease** Acrocyanosis while relatively uncommon among normal individuals is very common among mental disease patients¹⁸ (About 15 per cent in one series of 110 mental patients studied). It should be noted however that many mental patients of identical types may not have this syndrome and numerous cases have been seen in normals though more commonly in neurasthenic females than in other groups.

3 **Activity** Stern¹⁸ found that it occurred about 2½ times as frequently in those patients who habitually stood or sat about indifferent to chilling as in the normally active. In following his cases for four years he observed that 26 per cent showed decreased activity leading to greater cooling of the extremities with increased acrocyanosis. Twelve per cent showed increased activity with consequent warmth and decreased acrocyanosis. The remaining 58 per cent showed no changes either way.

4 **Endocrine Relationships** This is in a state of debate at present. We admittedly cannot accurately test the activity of many of the endocrine

glands. Stern¹⁸ does not believe there is an endocrine basis for this condition and he may be entirely correct. We have noticed in our series, however, a number of endocrine types of individuals and have had fairly consistently lowered basal metabolic rates. These have been in the low normal or somewhat subnormal range rather than extremely low. The sexual ratio is about equal¹⁸ in contrast to Raynaud's syndrome which occurs more frequently in the female (70 to 95 per cent of all cases according to the authority). Most cases occur between 20 and 45 years of age. The extremes in Stern's series were 1 and 67.

5. The relationship to the autonomic nervous system must be considered more carefully since interruption of these fibers by ganglionectomy benefits this condition according to White.¹⁴

6. Avitaminosis, especially deficiency in vitamin A, has been associated with this condition. High vitamin intake has been accompanied by improvement in a few instances. Much further work must be done before this relationship can be considered as established. At present skepticism is justified. Other factors such as blood pressure, blood count, Wassermann tests, blood chemistry, etc., have been unproductive in this regard.

It must be admitted that the fundamental etiological factor must be sought for further, the present status of knowledge in this regard being inadequate.

PHYSIOLOGICAL PATHOLOGY

Normal skin cooled to the point of cyanosis can be somewhat blanched if elevated to about heart level, demonstrating lack of venous obstruction. This is also true of acrocyanosis.²⁰ It was also demonstrated by Lewis and Landis that the white spot of Crocq disappears spontaneously and *leaves no trace* since it is due solely to displacement of blood from the area by the pressure used. Local trauma produces a red area within the cyanotic zone which appears to demonstrate a breakdown in what is otherwise arteriolar obstruction. This redness is greater in extent than the original area of the trauma. Furthermore, if the circulation to an acrocyanotic finger is occluded for from five to ten minutes following release the reactive hyperemia extends from 1 to 2 cm. proximal to the site of obstruction instead of being limited sharply to the obstructive point as in a normal finger. It is thought²⁵ that these phenomena are due to a ready diffusion of the H (histaminelike) substance to the sur-

rounding arterioles producing dilation. These phenomena fit into the hypothesis of Lewis and Landis that the mechanism of acrocyanosis is based on arteriolar obstruction. If the hand is cyanosed and a small part of it is warmed that area becomes a bright red. Similarly if a little histamine (1:3000 solution) is injected the local skin reddens with a rise in temperature.³ In the Raynaud syndrome this will not occur since the next larger set of arteries are involved and this phenomenon cannot occur until they have dilated.

In testing for this condition extreme cold 1 to 10° C (33.7 to 50° F) should not be used since in these as in Raynaud's patients and normal individuals the exposed parts become red due to arteriolar injury, dilatation and retarded deoxygenation of the blood.

Until recently it was felt that no organic lesions of the blood vessels were found in this syndrome. It was entirely reasonable however to suppose that the repeated contractions of the arterioles continued over a period of years might well produce certain changes such as hypertrophy of the media. Stern¹⁸ reports having demonstrated this to be true. He felt that the medial coats of all arterioles from 30 to 150 μ in diameter were definitely thickened at least to the upper limits of normal. He also found local edema and fibrosis of the skin together with dilatation and increase in number of the superficial capillaries. Layan²¹ claimed that various blood dyscrasias are found with acrocyanosis including prolonged coagulation time, lowering of the platelet count, etc. Stern¹⁸ checked these and many other factors—concluding that no abnormality had thus far been demonstrated.

The mechanism appears to be either due to local sensitivity of the small vessels to cold or to some vasomotor action producing increased arteriolar tone. Hixthausen²² and Lewis³ favor the theory that the vessels are especially susceptible to moderate cold reacting in a diffuse manner rather than specifically to extreme cold injury. They do not explain the source of the increased susceptibility. Lewis feels that this is localized to the arterioles to the skin since he claims that the cyanosis is not relieved quickly by a nerve block—as would happen if the condition were on a vasomotor basis. White¹⁴ on the other hand suggests a purely vasomotor basis since he claims that this condition is relieved as is Raynaud's syndrome by complete preganglionic section. Obviously this point must be clarified by further work.

TREATMENT

The treatment of acrocyanosis must thus far be directed at decreasing the arteriolar spasm. The following suggestions are therefore made:

1. Keep the patient and the part warm either by climate or local environment.
2. Keep the patient as physically active as possible within reason.
3. Reduce the mental strain to a minimum.
4. Iontophoresis using mecloyl (acetyl methyl choline chloride) may be helpful—(see section on Raynaud's syndrome for details).
5. Ganglionectomy—preganglionic root resection (recommended by J. White).
6. Vasodilating drugs: nitrates, pancreatic tissue extract, intramuscularly, etc. (empirical).
7. Thyroid extract has helped certain cases in our series if the basal metabolic rate is low.
8. A high vitamin regime empirically.

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CHAPTER LX

VASCULAR ANOMALIES

By G. DE TAKATS, M.D.

Introduction: Vascular anomalies occur when some part of the primitive vascular network is retained or transformed to a more adult arrangement, without undergoing definite stages of development (Baeder, 1866). Anomalous blood vessels are not uncommon. They may be due, as summarized by Arey,¹ to (1) choice of unusual paths in the primitive vascular plexuses, (2) to the persistence of vessels normally obliterated, (3) to the disappearance of vessels normally retained, (4) to incomplete development and (5) to fusions and absorptions of parts usually distinct.

It is hardly possible to understand the location and appearance of vascular malformations without a brief survey of the development of the vascular tree. The works of Evans,² Sabin,³ Woollard,⁴ McClure and Butler⁵ have given a clear description of the fundamental principles in the development of arteries and veins. What interests us here is whether or not certain clinical syndromes encountered among the vascular anomalies can be identified as belonging to certain stages of development in which the aberration from the normal took place.

Mont Reid⁶ has been the first to state emphatically that not only the congenital arteriovenous fistulas but the cirroid aneurysms (pulsating angiomas) and the simple angiomas are all due to abnormal arteriovenous communications. Thus, in the cirroid aneurysms, the communications are between the smaller vessels, while in the angiomas he considers them to be between arterioles and venules. None of these lesions are true tumors, as assumed by the older pathologists. Borst⁷ in his treatise on histopathology defined a true angioma as showing evidence of endothelial proliferation and formation of syncytial network. Most of the so-called angiomas, however, are only angiectasias, that is, dilatation and lengthening of arteries, veins or both. They represent developmental anomalies and their growth may be readily explained by a continuous filling from the arterial system with which they are more or less connected.

If as has been pointed out in a previous study⁵ one follows the classification of Woollard⁴ in recognizing three stages in the formation of an individual arterial tube and attempts to correlate them with various clinical pictures of vascular malformation not only may one assume that most of these vascular tumors are developmental anomalies but that the variations encountered are due to the arrest or modification of development in different stages of the normal process. Woollard recognized as a first stage a formation of capillary network. The capillary angiomas vascular nevi may be regarded as localized remnants of this stage. They remain harmless birthmarks until a sudden connection with the general circulation starts feeding them with blood in which case progressive cavernous dilatations develop. These grow so destructively that they may invade and necrotize bone and thus are often regarded as angiosarcomas without their histologic characteristics.

The second stage of Woollard is characterized by enlarged tubes showing island formation, coalescence and tendency to fuse. The first plexiform stage is followed by a retiform arrangement. Capillaries from which the flow of blood has been diverted atrophy. The selection of appropriate channels from the diffuse capillary bed results from the action of heritable patterns and the hydrodynamic factors incident to blood flow (Arey¹). The cavernous angiomas, the diffuse phlebectasias and phleboteriectasias described so fully by Sonntag⁶ may take origin in this second stage of development. Histologically these are numerous parallel vascular tubes which have not fused sufficiently and are connected with multiple communications. As Mont Reid⁶ so aptly remarked: "It is a wonder that direct communications between arteries and veins do not occur more frequently." Dr. Sabin¹⁰ stated that injections of pig embryos measuring 14 or 15 millimeters may still show slender connections between the middle segment of the internal jugular vein and the internal carotid artery.

It is only a slight step from this retiform stage to the persistence of multiple arteriovenous communications. Some patients exhibit a few tiny communications while others show such innumerable and unapproachable fistulas that as will be brought out later nothing short of an amputation can help.

Finally the third stage of definite stem formation with persistence of an anomalous primitive trunk may be correlated to the finding of a

peculiar vascular tube, running in an anomalous position in some extremities affected with vascular anomalies. I pointed out elsewhere⁸ that such a primitive vessel can be recognized by the finding of a number of longitudinal muscle fibers just below the intima which, according to Maximow,¹¹ occurs only in primitive, nondifferentiated vessels.

It may seem unnecessarily didactic to attempt such a correlation between the three stages of vascular development and the numerous clinical



FIGURE 1 Hypertrophic hemangioma. *A*, The patient is a three months' old infant; the tumor has been growing since birth. Obliteration of the tumor was achieved by the use of radium. *B*, The patient is a five year-old girl and the tumor of the leg has been growing slowly for several months. It was excised. (Cole and Elman: "Textbook of General Surgery," D Appleton Century Co, New York)

malformations. As a matter of fact, various stages of differentiation are frequently found in the same patient. But the clinical nomenclature of these vascular anomalies is so confusing that some working order helps to facilitate their understanding.

SIMPLE ANGIOMA

Simple angioma (angioma simplex) is most often found in the skin and subcutis of the head, although no region of the body is exempt. It is raised above the level of the skin, well circumscribed and composed of dilated capillaries and minute vessels surrounded by a circular arrangement of connective tissue. So long as these two elements show no pro-

liferation as in the hemangio endotheliomas or angiosarcomas, they do not have to be regarded as true tumors (Fig 1)

The clinical course of these small angiomas strawberry marks varies. The lesion is congenital and usually increases until the baby is about



FIGURE 2. Cavernous hemangioma seen at the age of 36 in S. R. A small bluish spot was noticed by his parents at the age of six months. At the age of 16 a physician found an angioma of the upper lip. The W. P. A. supervisor in a letter to the social service worker described his condition as "horrible, revolting and repulsive." It is hard to understand how Divine Providence could allow such an affliction to befall a human being. One wonders whether early attention to the birthmark might not have been effective. A. Before treatment. B. During progress of treatment. The external carotid artery has been tied above the superior thyroid artery; multiple injections of five per cent sodium morrhuate have been given into the cavernous dilations of the lids, cheek and upper lip; deep x-ray therapy was given externally and intraorally; a wedge-shaped resection of the upper lip was done. Patient is still under treatment; plastic work is contemplated on lid, lip and nose.

six months old. Then some of them disappear, some ulcerate, get infected, slough and heal, but most of them remain stationary and simply constitute a cosmetic problem. Of great importance, however, is the tendency of some of these tumors to exhibit suddenly a rapid active growth. Thus

in S. R., a 36 year-old man, a small bluish mark on the cheek rapidly involved the entire eyelid, cheek and upper lip, invaded the uvula, pharynx and buccal mucous membrane and constituted a real surgical problem (Fig. 2).



FIGURE 3. A B. a 21 year old girl had a large port wine stain limited almost entirely to the left half of the lower extremity, trunk and face. Her left leg was one and a half inches longer than the right but cold and cyanotic. She had a recurrent ulcer over the tibia which was grafted elsewhere but kept recurring. A diagnosis of congenital arterio-venous fistula with spontaneous thrombosis was made. A periarterial sympathectomy of the femoral artery and a paravertebral injection of alcohol to the lumbar sympathetic chain succeeded in warming up the leg and healing the ulcer. The leg has been useful and painless for over a year.

Most pediatricians advise treating the small "strawberry marks" between the age of three and six months with interstitial or external radiation of radium.¹² Usually from 4 to 12 treatments are necessary at monthly intervals. A slow regression is desirable; a complete disappearance requires several months of time. When seen at a later age electro-puncture, radium, or simple surgical excision may be performed.

PORT WINE STAIN

The port wine stain flat vascular nevus nevus flammeus is a capillary angioma. A reddish purple discoloration consists of numerous small capillaries in the midst of angioblasts truly the localized remnant of the capillary plexiform stage. They may be single or multiple some times involve an entire half of the body and are frequently associated with other vascular anomalies notably multiple arteriovenous fistulas (Fig. 3).

These stains usually do not spread but represent a difficult cosmetic problem. The use of radium and x rays in my experience has been followed by some blanching but no real disappearance. Dermatologists sometimes achieve excellent results with carbon dioxide.

CAVERNOUS ANGIOMA

The cavernous angioma one example of which is seen in Fig. 2 usually involves large skin surfaces but penetrates into the deeper structures. Histologically it contains multiple enlarged channels arteries and veins. The mass bleeds profusely and if injured leads to fatal hemorrhage. No bruit is heard over these masses and their connection with the general circulation is only moderate. The oxygen saturation of the blood aspirated from these masses is only moderately elevated from that of the normal venous blood.

The treatment consists of a combination of measures such as ligating the main artery excision and sclerosing injection of the accessible masses interstitial radium or deep x ray therapy for the internal masses. With a combination of these methods fairly satisfactory results can be obtained if recurrences follow they are usually easily controlled by sclerosing injections. Solutions of quinine and methame are preferable in those used in obliterating varicose veins.

CIRSOID ANEURYSM

Cirsoid aneurysm angioma arteriale racemosum constitutes a transition between the cavernous angioma and the congenital arteriovenous fistula. There are a number of large vascular tubes which pulsate and over which a bruit may be heard. They have a proximal nutrient artery and often originate from a simple angioma. Pregnancy muscular exertion and trauma are known to have initiated this transformation. The scalp face and upper extremities are most frequently affected. The

dilated veins may undergo thrombosis and phlebitic attacks have been seen in Case Number 1 of our first series.⁸ Nevertheless, they gradually progress and establish more and more connections between the vascular channels and the general circulation.

CONGENITAL ARTERIOVENOUS ANEURYSM

The congenital arteriovenous aneurysm consists of single, but most frequently multiple, connections between the normally developed major arterial and venous trunks. They occur in the carotid and subclavian area, but are most often seen on the lower extremities. They not only endanger the fate of the limb by their progressive enlargement but have systemic effects which differ in no way from those of a single, large traumatic arteriovenous fistula. They have been carefully described by Reid,⁶ Holman,¹³ Pemberton and Saint¹⁴ and others. Observations on these interesting cases together with a group of 16 partly unreported cases from my clinic established the following characteristics. The affected area is much warmer than the symmetrical area on the opposite side. The highest temperatures are around the communications, whereas distal to the fistulas the extremities are cold, cyanotic or may ulcerate. The proximal artery and vein are markedly dilated and may show degenerative changes. Distally the veins are prominent and filled with bright red, arterialized blood,*¹⁵ but the arteries are barely palpable or the pulsation may be absent. The venous pressure is greatly increased distal to the fistulas, but proximal to the fistula Reid¹⁶ could not confirm the elevated pressure noted by Holman¹³ and Ney.¹⁷

The effects of an arteriovenous fistula on the systemic circulation have been investigated and summarized by Matas,¹⁸ Reid⁶ and Holman.¹³ They are, briefly, as follows: The thrill and bruit may be heard with the naked ear, or with the stethoscope. They can be promptly stopped by compressing the proximal vein, for, as pointed out by Holman, the pressures in the arterial and venous channels are then equalized, which abolishes the whirling eddies of alternating high and low pressures. When the fistula itself is closed, there develops a rise in blood pressure and a fall in the pulse rate. Holman has interpreted this phenomenon as being due to an increase in blood volume, which has occurred as a result of a

* In Hazel F., a 16 year-old girl with multiple arteriovenous communications the right femoral vein carried a 92 per cent saturation with oxygen, whereas the arterial blood from the brachial artery had a 93.8 per cent saturation.

decrease in the circulatory bed. Closing the fistula restores the circulatory bed to its original status of a single system, the venous pressure proximal to the fistula decreases. That a cardiac dilatation and hypertrophy occurs with large arteriovenous fistulas whether traumatic or congenital has been shown repeatedly, experimentally and clinically that this is a 'reversible' heart is definitely proved.¹⁹ The argument centers however, as to the mechanism of its production. Lewis and Drury²⁰ thought

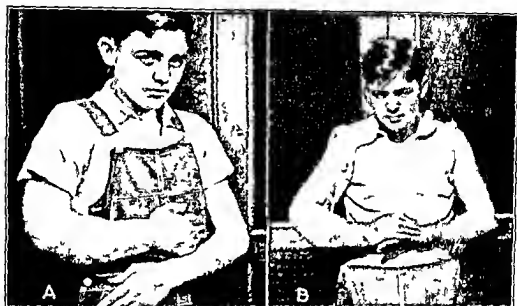


FIGURE 1. Qu 1, a 15 year old boy had an enlarged mottled purple colored right arm ever since birth. The saturation of venous blood with oxygen was 73.6 per cent on the right and 56.8 per cent on the left side. An attempt of intraarterial visualization through the brachial artery resulted in a large hematoma and a spontaneous thrombosis of a large number of anomalous vessels. The surgical resident could not find a normal brachial artery. Following this the arm became much smaller and the vascular dilations became less tense. On two subsequent occasions a long new silver wire was passed into the sacculations through an insulated spinal needle and a galvanic current was sent through the wire which resulted in coagulation of some of the vascular masses. The boy had a marked limitation of motion at the elbow and the arm is practically functionless. There was no enlargement of the heart. His arm may have to be amputated at a later date.

that the dilatation was due to insufficient coronary flow. Holman feels that the increased blood volume and rise of venous pressure proximal to the fistula is responsible. Reid has found that the cardiac output is markedly increased, that the circulation time was greatly accelerated when sodium cyanide was injected into the vein between the fistula and the heart, but retarded when it was injected on the distal side of the fistula. Reid was unable, however, to confirm the increase in blood volume and

rise in venous pressure proximal to the fistula as reported by Holman. Finally Lyster²¹ believed that the injury to the heart because of its overwork leads first to dilatation and then to hypertrophy.

It bears reemphasis that not only the traumatic but the congenital arteriovenous communications damage the heart and thus treatment is



FIGURE 5 L. R. a 20 year old male had a painless swelling of the left side of the face since birth. When stooping over or lifting a heavy weight the size of the mass definitely increased. A Before B Immediately after stooping over. Note the marked depression of the temporal bone in B. X ray showed irregularity of the malar bone.

indicated not only to relieve the embarrassment of peripheral circulation which leads to thrombosis, hemorrhage, ulceration and gangrene but to unburden the heart which unless the myocardium is permanently damaged will regain its normal size and functional efficiency.²²

Treatment The treatment of the above-described vascular anomalies depends on the size and location of the lesion. Ligation of the proximal artery, so disastrous in the traumatic fistulas is better born in

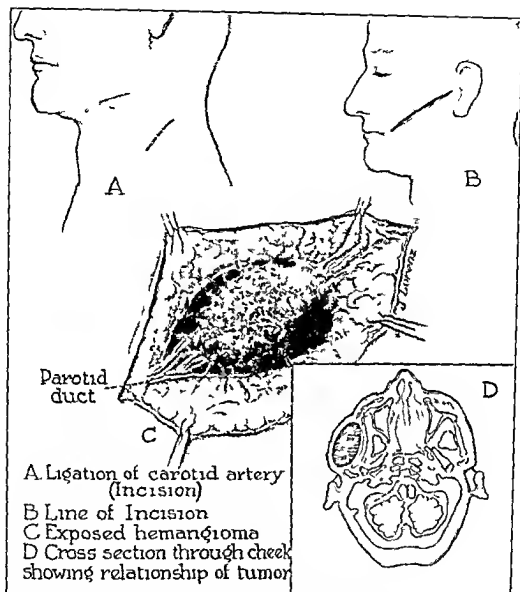


FIGURE 6 Same patient whose photographs are shown in Fig. 5. Following ligation of the external carotid artery the mass was exposed through an incision made from the angle of the mouth to the tragus; the mass was very vascular and bled profusely. A previous ligation of the external maxillary artery and injections of sclerosing solutions did not affect it at all. The parotid duct was visualized and saved. The mass seemed to be within the parotid gland which was substantiated by histologic sections. Fibers of the facial nerve were within the mass; all could not be saved. Ten weeks later, through a flap raised from below the mandible, the rest of the hemangioma was excised. Outside of the bone deformity, the mass has now disappeared.

the multiple arteriovenous communications, but done alone is never effective. In the large cavernous angiomas of the head and face, the external carotid artery may be ligated, the immediate shrinking of the mass has been striking in two of our cases, but the process is not arrested as blood is being fed through collateral channels. On the upper extremity a spontaneous thrombosis of the brachial artery was followed by a

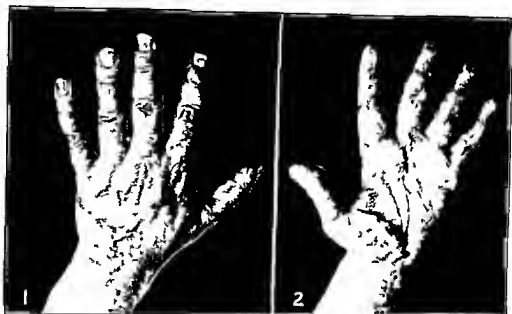


FIGURE 7 Left hand of Mrs P T K, a 58 year-old diabetic patient. Note the venous masses on the volar aspect of the finger tips. These became very painful during repeated attacks of thromboses and were incised for paronychia followed by profuse hemorrhage. The arteriovenous fistula was in the deep palmar arch and was excised without any disturbance of circulation (deTakáts Surg Gynec and Obst)

marked reduction of a cavernous angioma of the forearm and hand (Fig 4), on the lower extremity a spontaneous closure of a congenital fistula resulted in an atrophy and ulceration of the extremity (Fig 3). In the light of such experience deliberate ligation of the proximal artery is not advocated in vascular anomalies of the extremities, ligation of artery and vein in such desperate cases which are ready for amputation might be considered, but ligations of the external carotid artery may be done with impunity. When the internal carotid artery needs tying for cerebral angiomas, preliminary compression, preliminary tying of the common carotid and ligation of the internal jugular vein together with the artery are the best safeguards against cerebral damage.²³

Angiomas of the face, following preliminary ligation of the external carotid artery, may be attacked by surgical excision. These may have to be done in several stages and with care not to injure the parotid duct. When the skin or mucous membrane is diffusely involved interstitial radium or x ray therapy may help to shrink the mass. Sclerosing injections can be used in addition but only the cavernous mass forms large enough

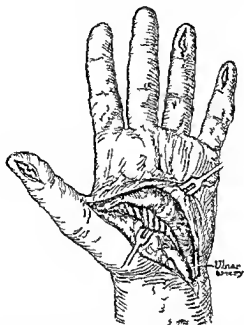


FIGURE 8 Sketch of findings at operation on Mrs. P. C. K. The ulnar artery was exposed. It was tortuous, sclerotic and entered a mass of veins which pulsated. Carrell clamps were applied both distally and proximally and the mass was excised. Many previous operations, ligation of the radial artery, excision of venous masses in the upper arm and forearm were unsuccessful in arresting the progress of the anomaly. Her hand has now been useful for ten years. (deTakatis Surg. Gynec. and Obst.)

individual pools (Figs 5 and 6). On the upper extremity the hand may be involved. recurrent attacks of phlebitis may produce painful nodules and may accelerate ulceration (Figs 7 and 8). In the case of a young man a diffuse superficial phlebectasis carried highly oxygenated blood with a lot of phleboliths but an intrarterial injection of skiodin failed to reveal any arteriovenous communications (Figs 9 and 10).

Convulsed masses of venous dilations existing since birth and associated with a port wine stain represent congenital anomalies and are often mistaken for varicose veins. In Fig. 11 a sketch taken from the findings at operation demonstrate why simple injections do not ordinarily suffice. Complete excision, if necessary in several stages is preferable.

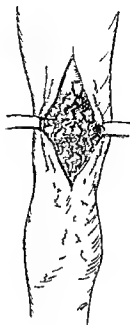


FIGURE 9 Congenital arteriovenous fistula seen in F J 17 year-old boy. Anomals had been noticed shortly after birth. The whole mass was suprafascial and could be readily excised. His main complaint was pain on exercise and intermittent claudication of the upper extremity.



FIGURE 10 Intravascular visualization of the brachial artery and its main branches by skiodan. Case of E. J. whose photograph is shown in Fig. 9. The brachial radial interosseus and ulnar arteries are seen together with a phlebectasis in one of the vascular dilatations. In spite of the high oxygen saturation in the sinus blood, this film did not help to locate the arteriovenous communications.

Great difficulty is encountered in the treatment of diffuse vascular anomalies of the lower extremities because they are usually presented at a late stage when the vascular dilatations permeate the entire cross section of the limb including the bone marrow, and only amputation offers



B

FIGURE 11 A local red vascular mass in the popliteal fossa of Mrs. M. C., age 42. This spongy mass was present ever since she could remember, was diagnosed as varicose veins and repeatedly injected without success. There was no visible enlargement of the major or minor saphenous vein. There seemed to be no pulsation in this mass; it could be readily emptied on pressure and seemed to fill from below. At operation a large number of tortuous parallel vessels were excised; the vessels had hardly more than an endothelial lining. The endothelial cells were large and not quite regular. (deTakáts, Surg., Gynec. and Obst.)

relief. Reid⁶ published such a case. In our earlier cases I performed radical excisions of all visible vessels in as many as four to six stages; these operations are very vascular and shocking (their case reports have been published in 1932).⁸ More recently a few ligations were done at a time under a tourniquet with sclerosing injections given during the operation; the patients stay in the hospital only a few days and reenter

every few weeks, it has taken three to four years for a satisfactory control of the anomaly, but the process seems to be well arrested (Fig 12)

Especially interesting is the finding of large anomalous trunks at atypical locations showing the histologic structure of primitive vessels (Figs 13 and 14) These I have now found in three patients It may well be that they represent a nonabsorption of primitive stems



FIGURE 12 A. P. a 19 year-old girl had pain in her right ankle and a large recurrent ulcer over the tibia for 12 years. She was repeatedly diagnosed and treated as having osteomyelitis. Her femoral artery showed no abnormal communication but the saphenous vein was large and carried highly oxygenated blood. It was tied. The ulcer was excised and covered with a thick Thiersch graft. Multiple ligations were done and large primitive vascular trunks were excised. The treatments lasted for over three years. Now the anomaly seems to be arrested although the swelling seems permanent and occasional bandaging is necessary. Note healed ulcer at middle third of tibia and the scars of multiple incisions. Several small port wine stains at and above knee.

As vascular anomalies of the extremities exhibit increased growth and frequently marked edema they must be differentiated from hemihypertrophies without vascular involvement (Fig 15) or congenital lymphedemas which are often associated with vascular birthmarks (Fig 16)

While occurring most frequently on the head and extremities vascular anomalies may be encountered in any part of the body. Angiomas of the kidney, liver and vertebral bodies are comparatively common. Cushing and Bailey²⁴ have published a classic monograph on vascular

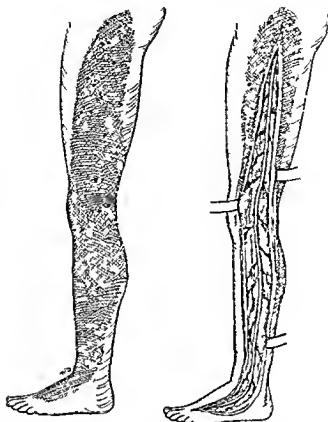


FIGURE 13 Case of A D The shaded area represents the extent of the cutaneous birthmark while the small black dots illustrate the distribution of multiple capillary angiomas which bled repeatedly The drawing on the right illustrates the large anomalous trunk under the superficial fascia It was thick, did not pulsate, but had the size of about the common iliac artery It gave off numerous branches medially and laterally and was excised in three stages (deTakáts Surg Gynec and Obst)



FIGURE 14 A 13 cm long segment of the anomalous blood vessel in case of A D The lumen was partly obliterated It had the thickness of an artery but was very poorly differentiated into layers The media contained adjacent to the intima a large number of longitudinal muscle fibers which according to Maximow occurs in primitive nondifferentiated vessels No elastic membrane was seen

tumors of the brain. They represent from one to two per cent of intracranial tumors. Dandy²⁵ and Matas²⁶ have recently discussed aneurysms of the circle of Willis, roughly half of which are due to congenital defects in the walls of the vessels. As Matas has pointed out, these aneurysms

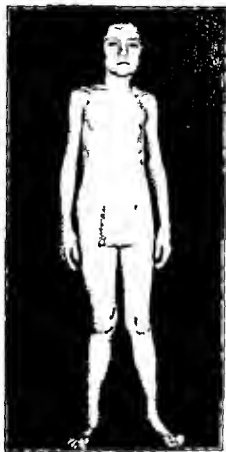


FIGURE 11. L. F., a 13 year-old girl with a hemihypertrophy involving the right upper and lower extremities, the scapula and pelvic girdle. Temperature readings, infrared photographs and oscillographic curves failed to reveal any difference in the vascularity of the two halves of the body. The right lower extremity is $1\frac{1}{2}$ inches longer than the left.

should not be confused with the extremely small, multiple military aneurysms which under the strain of hypertension rupture and cause intracerebral hemorrhages as first described by Charcot and Bouchard (cit 26). The discussion of congenital vascular lesions of the brain, including Fig. 17, has been supplied by Dr Percival Buley.

The commonest vascular anomaly within the intracranial cavity is a congenital weakness of the walls of the arteries of the circle of Willis

which results in aneurysmal dilatation. The most frequent site for these congenital aneurysms is the point of origin of the anterior cerebral artery. Rupture of this aneurysm causes a typical clinical picture (Symonds 27) characterized by pain over the eye followed by obnubilation and finally



FIGURE 16 J. G. a 32 year-old woman believes to have noticed an enlargement of her left leg at the age of 8 years after scarlet fever. She had a number of small cutaneous nevi around the ankle. The left leg was 15.0 inches longer than the right and was warmer. The edema was remarkably evacuated by elevation and bandaging. On excising the redundant skin together with a large window in the fascia a large anomalous lymph channel together with degenerated nerve plexuses was excised. This is a congenital lymphangioma with associated anomalous nerve tissue and a vascular birthmark.

coma. There is stiffness of the neck because of irritation of the meninges from the extravasated blood in the subarachnoid space. Rarely such congenital aneurysms may occur elsewhere in the intracranial cavity.

A rare congenital telangiectatic anomaly is known as Sturge-Weber disease. It usually manifests itself in childhood by epileptic attacks. On examination the child is found to have a facial naevus and x-ray photograph of the skull discloses concentric tortuous lines of calcification usually

ally in the occipital region. This calcification was formerly supposed to lie in the walls of the telangiectatic vessels but has been shown by Krabbe²⁸ to be mainly in the adjacent gyri of the cerebral cortex.

An anomalous development of the capillary bed in the cerebellar region occurs in Lindau's disease resulting in the formation of a hemangiomatic tumor which is nearly always associated with a large cystic cavity filled by yellowish fluid of high protein content. This pathological lesion very often occurs with the hemangiomatic anomaly of the retina known as von Hippel's disease. That the two lesions are part of a heredi-

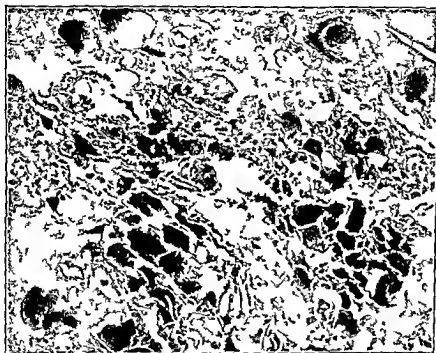


FIGURE 17. Cavernous hemangioma from the frontal lobe. Hematoxylin-eosin. $\times 10$.

tary pathological complex was first demonstrated by Lindau²⁹ hence the name Lindau's disease.

In addition anomalous tangles of larger blood vessels may occur (Cushing and Bailey²⁴) and depending on the structure of their walls are known variously as racemose angiomas, arterial or venous as cavernous hemangiomas or as capillary telangiectases (Fig. 17). They give evidence of their presence often by epileptic attacks although in the racemose angiomas arteriovenous fistulas may occur resulting in an intracranial bruit. The capillary telangiectases may occasionally be calcified.

sufficiently to be seen in an x-ray photograph of the skull (Levin and Michael³⁰)

Aberrant vessels of the kidney are often thought of by urologists as being the cause of a ureteral link. Small angiomas of the viscera are usually found post mortem and produce no clinical symptoms.

One can hardly close a chapter on congenital arteriovenous communications without at least mentioning an intriguing group of small tumors originating from small arteriovenous anastomoses which are normally present in fair numbers at the nail bed, the volar cushion of fingers in the palm of the hands and on the toes. These small shunts serve the purpose of heat regulation and may be involved in diabetes, arteriosclerosis or Buerger's disease.³¹ Small tumors originating from them have been called neurovascular glomus tumors by Masson.³² The lesion is so characteristic and yet has been unrecognized so often that attention should be drawn to it. These small purplish tumors are exceedingly painful and pressure on them elicits paroxysmal attacks of pain. They are occasionally erectile and may double their size on stroking. They may produce reflex vasomotor and sweating phenomena. In three personally observed cases the growth was unrecognized for 10, 12 and 42 years respectively. Simple removal is curative. In a total of 70 cases reviewed in the literature no recurrences were reported.

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CHAPTER LXI

VARICOSE VEINS

By G. DE TAKATS, M.D.

Introduction: Dilatation, elongation and tortuosity of veins may occur in any part of the body. Characteristic clinical syndromes are produced by varices of the central nervous system, of the esophagus, of the broad ligament and urinary bladder, of the spermatic and of the rectal veins. The varicosities of the superficial venous network of the lower extremities, however, are of the greatest clinical interest and in this discussion only the involvement of the saphenous system will be considered.

Ever since Hippocrates it was assumed that thick bile and mucus or "melancholy" blood was contained in varices and Ambrose Paré (1579) warned "not to meddle with such as are inveterate, for of such being cured there is to be feared a reflux of the melancholy blood to the noble parts, whence there may be imminent danger of malignant ulcers, a cancer, madness or suffocation." The last two complications suggest sepsis and pulmonary embolism, which must have been frequent after Paré's ligations in the preaseptic era.

ETIOLOGY

Gradually, a mechanical conception of the etiology of varicose veins has been evolved, starting with Harvey's demonstration of a mechanical form of circulation. While much argument and misunderstanding existed in regard to the position and function of valves, it can now be stated with certainty that dilated veins result fundamentally from two causes: (1) A valvular incompetence, which may be congenital or acquired as a result of trauma or inflammation; and (2) a block of certain venous channels resulting in compensatory enlargement of others. While the first variety is seen in the primary juvenile type of varicosities, the second is encountered after obstruction of the femoral or iliac veins as a collateral circulation.

When man assumed the erect posture, an unusual strain was placed on the return circulation from dependent parts. Two mechanisms were
(1770)

gradually evolved to compensate for the upright position. The vasomotor system prevents a fall in blood pressure on standing; in fact a slight overcompensation takes place in the normal individual as shown by the observations of Grace Roth.¹ This compensatory vasoconstriction is under the control of the pressor receptors in the carotid artery in the aorta and other vessels when a bilateral denervation of the carotid sinus was done. Capps and I² observed a permanent postural hypotension.* The other mechanism which prevents large amounts of blood from accumulating in the dependent parts of the body are the valves of the venous system whose function is to give irreversibility of direction to the blood stream in the veins. Incompetence of valves in the superficial veins of the limbs results in the stagnation of large amounts of blood and a marked rise in local venous pressure. The effective circulating blood volume can be reduced to such an extent that vasomotor activity is unable to maintain systemic blood pressure and a postural hypotension develops which can be readily abolished by tight bandaging. The limbs thus serve as blood depots from which the blood cannot be mobilized as readily as from the spleen or liver. The diminution of effective blood volume that occurs on standing because of the increased filling of the vessels of the abdomen and limbs is measurable even in the absence of varicose veins especially in young healthy or convalescent individuals. There is a decrease in heart volume, minute volume and stroke volume. This latter may decrease to 50 per cent of its value on changing posture.³

The adaptation to the erect posture is not uniformly adequate in the saphenous system; there is a marked variation in the number and position of the bicuspid valves. In addition the anatomic course of the saphenous veins deprives them of an important aid in venous return, namely the milking effect of muscular activity. As the veins are unsupported between the skin and the fascial layer they are more apt to be exposed to increased venous pressure. Should the femoral valve proximal to the sapheno-femoral junction be congenitally absent the difficulty of venous return in the erect posture becomes even more pronounced.

Heredity seems to be important in the development of varicose veins. A constitutional weakness of the connective tissue is often encountered in other regions of the body. Such patients have hernias, fallen arches, suffer from visceroptosis and the vulnerability of the vascular system may

* The same is observed after the extensile lateral splenic nerve section of Smithwick.

be evident from cutaneous nevi or varices in the nasal septum. The palpable vessels are soft, easily compressible and the blood pressure low. A positive family history of varicose veins could be elicited in approximately 70 per cent of any large series. When varicose veins are seen in young people, both parents are usually affected.

The undue strain of prolonged motionless standing is another factor in raising venous pressure in the saphenous system. Thus waiters, luncheon waitresses, street car conductors and policemen are predisposed by occupation and their existing varicosities are aggravated. Constricting garters obviously increase the difficulty of venous return. When venous pressures were determined in the horizontal sitting and standing position with and without constricting garters, striking differences were noted (Tables I and II).

TABLE I
DETERMINATIONS OF VENOUS PRESSURE IN VARICOSE VEINS

Case	Standing	Sitting	Horizontal	Comment
1	108	69	19	{ Thrombi in communicating veins
2	76	44	8	
3	210	—	63	
4	91	61	37	
5	†	†	187	
6	80	57	10	
7	85	61	12	
8	105	59	13	

These figures are not corrected to heart level as the actual pressure exerted on the wall of the vein was estimated. The determinations were made by the indirect method of Eyster. The figures represent centimeters of water.

†The pressure could not be estimated as the Eyster apparatus only registers to 300 cm of water. (deTakáts, Quint, Tillotson and Crittenden, Arch Surg.)

TABLE II
EFFECT OF CONSTRICTING GARTER ON VENOUS PRESSURE, CARBON DIOXIDE AND OXYGEN CONTENT IN SAPHENOUS BLOOD

Case	Pressure	Carbon Dioxide	Oxygen	Hemoglobin
1 without garter	105	49.67	9.98	14.76
with garter	130	49.35	6.46	14.76
2 without garter	89	47.90	13.62	13.23
with garter	115	48.30	6.96	13.23

A rubber garter was applied above the knee for 15 minutes, the patient remaining in the standing position. The pressures are expressed in centimeters of water, the carbon dioxide as l. oxygen in per cent by volume, the hemoglobin in grams per 100 cc. of blood. The hemoglobin was determined to test for possible dehydration. (deTakáts et al., Arch Surg.)

Other causes for increasing venous pressure are traumatic rupture of valves pressure of lymph glands or pelvic organs, straining with constipation and pregnancy. Pregnancy interferes with the venous back flow of the extremity by the pressure of the enlarged uterus on the iliac veins. But more important than this is the greatly increased volume of venous blood flowing from the hypogastric vein which produces a relative incompetence and obstruction in the external iliac vein possibly endocrine factors may also play a role in the relaxation of venous tone.

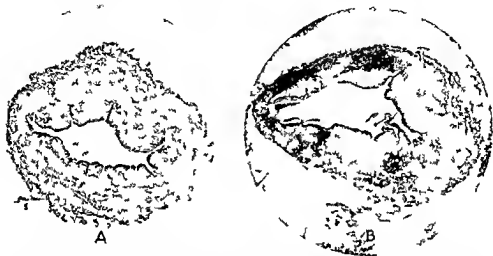


FIGURE 1 Internal saphenous vein close to saphenofemoral junction. A Thickened medial hypertrophy of media. The vein is arterialized. B Vein from a later stage markedly dilated. Fibrous tissue replaces the muscular element. At certain points the media disappears entirely. The intima is hypertrophic (deTakáts, Quitt, Tillotson and Crittenden, Arch Surg.)

Finally, the effect of postpartum postoperative or postinfectious thrombophlebitis on the development of varicosities must be considered. The obstructive clot may be in the iliac, femoral or communicating veins. It produces new collateral channels with the formation of varicosities of atypical course. Later when the clot canalizes there may result a destruction or shrinkage of valves at the site of the clot. The patient then suffers from a valvular incompetence of the deep or communicating veins with resulting postural venous hypertension. The work of Turner Warwick⁴ and Edwards⁵ has pointed to this mechanism of deep venous insufficiency which in my experience is more frequent than a permanent deep venous obstruction.

The morphologic changes encountered in varicose veins can be readily explained as the results of increased venous pressure and slowing of the



FIGURE 2 This leg has been emptied of venous blood by elevation. A rubber tourniquet was then applied tight enough to compress the internal saphenous vein. On lowering the leg a sudden filling of the medial group of varicosities on the calf took place. The communicating veins between the deep and superficial systems are incompetent here.



FIGURE 3 A 52-year-old woman's lower extremities. She has had no history of phlebitis after childbirth but there is a progressive venous valvular insufficiency with an opening of the subpapillary venous plexuses.

(1774)

blood stream. The muscular tube of the saphenous vein first responds with a hypertrophy, later a dilatation, elongation and tortuosity (Fig. 1). There is a more or less constant inflammatory reaction in and around the walls of varicose veins indicating that bacteria circulating in the blood



FIGURE 4. Dry atrophic skin, scaly and pigmented. The lighter areas are the sites of healed ulcers. Note the fallen longitudinal arch and bunion, both of which are often associated with the varicose state.

stream are readily deposited here and may remain in a latent stage for many years. Sudden strain, direct trauma or the injection of sclerosing substances are capable of activating this "resting infection" and thus many of the unexpected and unexplained cases of phlebitis can be accounted for.⁶

Such a resting infection of varicose veins may also act as a focus of infection, maintain a rapid sedimentation rate and produce reactions

especially in joints and muscles. Thus in the treatment of an infectious arthritis or myositis, a latent phlebitis in a varicose vein should be considered as one of the possible foci of infection.

The venous insufficiency of the saphenous system is a progressive lesion. More and more valves become incompetent in the major or minor saphenous vein or in the perforating veins, which connect the deep and superficial veins (Fig. 2). Finally the venous stasis may spread into the



FIGURE 5 Area of hyperkeratosis at the site of previous ulceration. These areas are itchy and painful. The varicosities above the lesion have not yet been treated.

subcutaneous network or into the intradermal subpapillary plexuses and the so-called "spider bursts" or "racket bursts" appear (Fig. 3). This progressive venous insufficiency results in nutritional disturbances of the skin and subcutaneous tissues. The skin becomes atrophic, pigmented, dry, scaly and is readily subject to eczema (Fig. 4). Because of the poor oxygenation of the tissues, their resistance to trauma or infection is slight. In addition, the small veins of the skin and subcutaneous tissue readily become occluded by thrombi. Such segmental thrombi with a periphlebitic induration are often the site of ulceration; the atrophic, thin skin easily breaks down above the thrombosed area and forms the varicose ulcer. Slight trauma may be the immediate cause of such an ulcer. The common site of varicose ulcers is on the inner side of the calf, two or three finger breadths above the inner ankle. They may appear above the external ankle or below either ankle. At this latter site they are most resistant

to treatment. Other patients exhibit areas of hyperkeratosis at the site of previous ulcerations (Fig 5)

SYMPTOMS AND DIAGNOSIS

The early symptoms of progressive venous insufficiency are a tired heavy sensation in the legs cramping of the calves at night or in cold

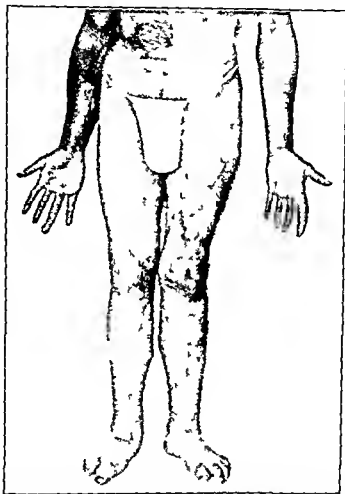


FIGURE 6 Congenital vascular anomaly in a 22 year-old student who has been treated for several years as having varicose veins. Together with a marked dilatation of the internal saphenous vein and its tributaries the patient had several cutaneous birth marks and a marked hypertrophy of both feet with a beginning elephantiasis of the toes. Note the abnormally long thick fingers. The venous blood carried highly oxygenated blood. Multiple vein ligations and injections resulted in a satisfactory arrest of this anomaly.

water and swelling of the ankle or the dorsum of the foot. Young women appear complaining of unsightly blue markings along the calves of the leg which are more noticeable just before menstruation. When the venous dilatations reach a certain stage the traction on the saphenous nerve may

produce painful radiation along the course of the nerve. The extent of the varicosities by no means parallels the severity of symptoms as enormous dilatations are often symptomless and a few hardly palpable varicosities if slightly thickened may produce much discomfort. Most of the symptoms, however, are due to complications such as phlebitis, ulceration, eczema or hyperkeratosis.

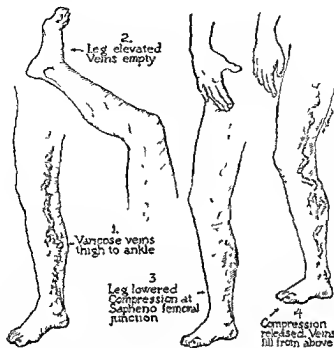
Offhand the diagnosis of varicose veins is so obvious that little need to be said about it. However venous dilatations occur in arteriovenous fistulae and most of the cases coming to my attention have been treated as varicose veins for a long time (Fig 6). The distinguishing features of this type of lesion will be discussed in Chapter LX. Compensatory venous dilatations following deep venous thrombosis are not true varicose veins and do not follow the course of internal and external saphenous veins but show atypical convolutions chiefly on the lateral aspect of the thigh, gluteal region and dorsum of the foot.

A frequent error is made in diagnosing varicose veins as a source of complaints when other conditions are responsible for the symptoms and varicose veins are just coincidental. Thus flat foot, genu valgum, arthritis of the knee, sacroiliac and lumbosacral arthritis, spondylolisthesis or true sciatica may be overlooked. Compression of the lumbosacral plexus by inflammatory or neoplastic diseases and compression of the spinal cord may be missed in a superficial examination and the varices made responsible for all the symptoms. Femoral hernia and the rare lymphocele of thigh may be mistaken for varicosities. Small hernias of the tibialis anticus muscle which occur on the lateral aspect of the lower leg and are painful because of the traction on the superficial peroneal nerve have been repeatedly taken for varicose veins.

TEST OF VENOUS CIRCULATION IN THE VARICOSE EXTREMITY

The condition of the valves in the superficial and communicating valves and the patency of the deep veins must be tested before any treatment can be undertaken. The Trendelenburg test (Fig 7) gives information regarding (a) the incompetence of the saphenous valves close to the groin and (b) the incompetence of the communicating veins. The leg is elevated and the superficial veins are emptied. Next the saphenous vein is compressed at the region of the saphenofemoral junction. The patient now stands up with the saphenous compression still maintained.

when the veins in the lower thigh and calf remain collapsed in the standing position, one has good evidence that reflux of venous blood only occurs from above, *i e.*, through the saphenofemoral junction. However, when the veins below the compression suddenly fill on assuming the erect posture, the blood must flow in from the deep veins through incompetent valves in the communicating veins. The site of these—there



TRENDELENBURG TEST

FIGURE 7 The Trendelenburg test. The leg is first elevated to empty the veins and pressure is applied at the saphenofemoral junction. The patient then stands up with the compression maintained. Note the collapse of the vein below the finger. When compression is released, the vein suddenly fills from above. (deTakats on Varicose Veins in "Text-book of Surgery," edited by Frederick Christopher, 2nd Edition, W. B. Saunders Company, Philadelphia and London.)

may be few or many—can be determined by repeating the Trendelenburg test with a digital compression which is gradually lowered until a collapse of the veins in the calf is obtained. These incompetent communicating veins often reveal themselves by a sacular varicosity, a "blowout" on the thigh and are frequently found at the middle and lower third of the thigh (Fig. 8). Mahorner and Ochsner have especially stressed their importance.⁷ But valvular incompetence is also found in the calf and Linton⁸ has recently studied them in great detail. Kosinski⁹ described the variations of the short saphenous system.

The proper performance of the Trendelenburg test and its interpretation is important as the rational treatment of the individual case will greatly depend on it. The patency of the deep veins is tested by the method of Perthes (Fig. 9). Following the constriction of the saphenous

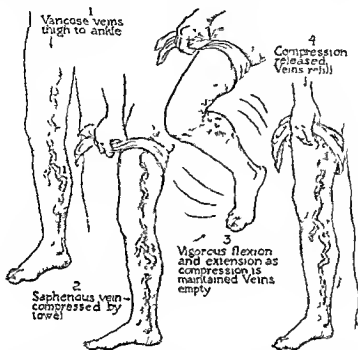


FIGURE 8 A blowout at the lower third of the thigh. When the patient is asked to cough the inserted finger feels an impulse from the deep veins even if the saphenous vein is compressed at the saphenofemoral junction. Note again the relaxed arch—especially the transverse arch—and a lunation.

vein by a tourniquet, vigorous muscular exercise, such as bending and extending the knee is carried out ten times. If the deep veins are patent blood is sucked into the deep veins and the superficial varicosities diminish in size. When the pressure of the tourniquet is suddenly released the filling from above demonstrates the amount of blood aspirated into the deep veins. In case of deep venous obstruction or increased deep venous pressure no diminution of the varicosities will take place. The test may

give a questionable result when so many communicating valves are in competent that a steady reflux occurs from the deep to the superficial veins.

Latent infection in the superficial or deep venous system should always be looked for before instituting treatment. Manifest phlebitis



PERTHES TEST

FIGURE 9 The Perthes test. A towel is thrown around the thigh and twisted so as to compress the saphenous vein. Vigorous flexion and extension is carried out ten times. Note how the veins collapse following exercise. When the pressure is released the veins fill again from above, demonstrating the amount of blood aspirated into the deep veins during exercise (deTakáts *Varicose Veins in Textbook of Surgery*, edited by Frederick Christopher, 2nd Edition W. B. Saunders Company, Philadelphia and London.)

is discussed in Chapter LVI. But a latent phlebitis is often present in patients with little or no subjective symptoms. Its recognition is important for infection may be readily stirred up during treatment and may result in massive thrombosis, weeks of enforced bed rest and pulmonary embolism. Most of the complications following the injection treatment of varicose veins can be traced to an activation of a latent phlebitis.

When the latent infection is in the superficial veins, the palpable veins are thickened, tender to touch and small phleboliths are felt. The skin over these veins is definitely warmer than elsewhere. Changes in weather bring on an increased sensitivity in the veins just as in rheumatic

joints. The sedimentation rate is accelerated. A simple puncture of such a vein may provoke a segmental phlebitis. The sclerosis of valves gradually leads to incompetence.

Latent infection in the deep veins, especially in the tributaries of the common iliac vein, manifests itself in recurrent attacks of mild edema of the limb or groin, frequent micturition, and the so-called "pelvic neuritis" which occurs often after a manifest pelvic phlebitis. This pain usually radiates along the sciatic and less often along the femoral distribution and is probably due to thrombosis of the veins accompanying nerve trunks or thromboses of the branches of the hypogastric vein, producing spasm of the pyriform muscle and thus producing sciatic compression.

Finally latent infection in the muscle veins of the calf, following trauma or deep phlebitis and producing valvular incompetence of the communicating veins must be watched for. Thromboses of the muscle veins, as pointed out by John Homans,¹⁰ are more apt to produce pulmonary embolism than any other form of thrombosis. Injections into such veins produce localized swelling and tenderness of the calf muscles and may stir up a real thrombophlebitis. Swelling of the calf, increased skin temperature over such areas and increased sedimentation rates are the warning signals.

It is impossible to give an arbitrary time for the subsidence of a latent phlebitis. Foci of infection must be eradicated. Locally, mild doses (100 to 120 r units) of roentgen-ray treatment and, in superficial phlebitis, iontophoresis with mecholyl hasten to clear up the infection. The prolonged use of adequate elastic compression with rubber bandages or gelatin casts hasten the quiescence of the phlebitis in the muscle veins.

I have dwelt at considerable length on these latent, "resting" infections because most of the untoward consequences of the treatment of varicose veins occur through the nonrecognition of latent infection and its activation during treatment. Edwards,¹¹ however, feels that the inflammation is not a bacterial one and that the phlebitis of the varicose vein should be treated as if the phlebitis were absent.

COMPLICATIONS OF VARICOSE VEINS

Varicose veins tend to progress by forcing open more and more valves in the saphenous and communicating systems. When the chronic venous insufficiency reaches the venules of the skin, the subpapillary

plexus and its tributaries are flooded with blood and produce the unsightly spider bursts or racket bursts. These stellar patterns of small cutaneous veins may occur in the absence of marked valvular incompetence and must be due to the atony of muscular mechanisms often seen in women around puberty and menopause.

The skin in progressive venous insufficiency becomes dry, thin and scaly. Later it becomes pigmented and is easily vulnerable. In the presence of a thrombophlebitis of the subcutaneous and cutaneous varices



FIGURE 10. Typical varicose ulcer on the inner aspect of the calf with a venous pool above the ulcer. There is a second small ulcer below the valvular incompetence. It is more difficult to heal than the large one. Note the absence of a fibrin or lymphatic stasis. (Takács, Surg. Gynec. and Obst.)

huge patches of induration develop, the skin over these is a glossy, dark red to purple and later takes on a dark brown color. The subcutaneous induration is the result of edema, lymphostasis and gradually results in an extensive fibrosis of the tissues which only adds to impaired nutrition. A weeping or dry eczema or a ringworm infection is not infrequent.

The skin breaks readily at the site of previous pigmentation or induration as a result of mild trauma or following a thrombosis of a cutaneous vein above which the skin ulcerates. The common site of ulcers is on the inner side of the calf, two or three finger breadths above the inner ankle (Fig. 10). They may appear, however, over the external ankle or below the ankles. At this latter site they are especially painful and resistant to treatment.

While some large ulcers are comparatively painless some very small ones especially at the level or below the ankles are excruciatingly painful. The cause of this pain is found in small neuromas embedded in the fibrous base of the ulcer or an actual encroachment of the ulcer on the

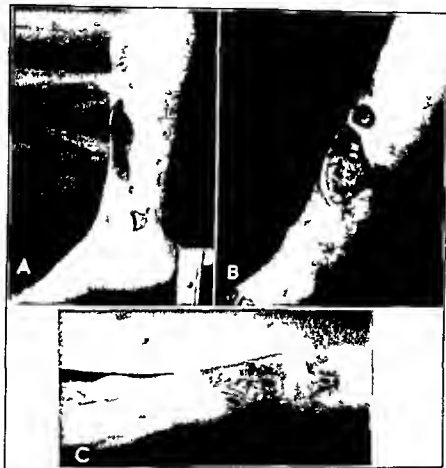


FIGURE 11 A Arterio-occlusive ulcer B Ischemic ulcer C Traumatic ulcer

saphenous or posterior tibial nerves. Such ulcers produce paroxysmal attacks of pain, arterial spasm and sweating not unlike a cruralgia.

Other ulcers are less painful but become infected with organisms which retard its healing. Smears and cultures taken from the base of the ulcer may reveal hemolytic streptococcus, hemolytic staphylococcus, diphtheria bacilli and many other organisms such as Meleney's microaerophilic streptococcus, all of which require special treatment. Generally speaking the bacteriology of these ulcers is not remarkable and

should only be studied when the ulcer is refractory to the usual forms of treatment

Varicose ulcers behave and progress similarly to duodenal ulcers. They may be superficial with soft edges, healthy granulations and a marked tendency to heal, or they may be inflamed with a hard indurated

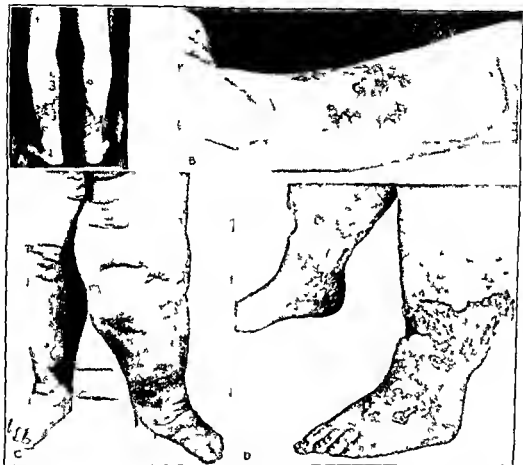


FIGURE 12. A Superficial ulcer on a leg with ringworm infection on the ankle. B Tuberculous ulcer. C Elephantiasis with small ulceration. D Neglected thrombotic ulcer with lymphostasis. (deTakáts, *Strg. Gynec. and Obst.*)

margin, a glossy, pale or greenish necrotic base and may be resistant to treatment. If an ulcer resists treatment, one should look for (1) poor arterial circulation, (2) extensive scarring and lymphostasis around the ulcer, (3) a too large defect to permit spontaneous epithelialization, (4) a specific bacterial infection (diphtheria, Meleney's streptococcus with symbiosis) and (5) the possibility that the ulcer is not a varicose or thrombophlebitic ulcer.

Just because there are a few veins present not every leg ulcer is due to venous stasis or inflammation (Figs 11 and 12). Thus lues, tuberculosis, mycotic infections, mycosis fungoides and trophic ulcers should be considered. Out of 500 leg ulcers my associates and I have recognized three luetic, two tuberculous ulcers and one case of mycosis fungoides. Obviously the incidence of these will vary according to localities. The distinction between varicose and thrombophlebitic ulcer is often made. The latter is characterized by edema, induration and lymphostasis around the ulcer. Hidden below all this there is valvular incompetence of the communicating veins flooding the area with stagnating poorly oxygenated blood. The varicose ulcer on the other hand may show a remarkable absence of these complicating factors and therefore is more responsive to treatment.

Another complication of varicose veins is the rupture of a vein with consequent hemorrhage. This usually occurs from a thin walled unaffected vein and is very rare in my experience because the superficial veins are more apt to develop thick fibrous coats and thromboses thus protecting themselves from hemorrhage.

Thrombophlebitis of the varicose vein is a frequent and important complication. I have referred to its latent form; it is discussed in Chapter LVI.

TREATMENT OF VARICOSE VEINS AND COMPLICATIONS

The aim of any type of treatment is to relieve the increased hydrostatic pressure. Palliative measures consist of a snugly fitting elastic support which produces tight but even pressure and should reach above or at least to the level of valvular insufficiency. This ideal can seldom be accomplished by stockings on the market as they are invariably too short. When made to order stockings of elastic yarn or mercerized silk should extend to the groin. Elastic crepe, elastic adhesive and rubber bandages may give good support and are more often used by men. Women frequently object to their appearance. Ureter's paste boot consisting of zinc oxide, glycerin, gelatin and water has its greatest usefulness in chronic indurated ulcers or postphlebitic indurations. Bandages saturated with this mixture are now on the market.

Such treatment by elastic support is advised in a patient whose age, infirmity or prejudice against other procedures prevent the use of any

other method. In addition women in the last few months of pregnancy, or patients during and after other forms of treatment obtain considerable relief from a well applied elastic support.

Treatment by rest, elevation and hot boric dressings may become necessary in the presence of acutely inflamed veins or ulcers. Within a few days however, the patient may get up and walk. Ambulatory treat-

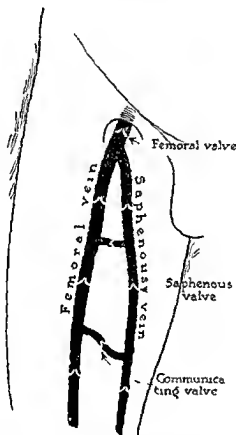


FIGURE 13 The valvular mechanism of the veins of the lower extremity. There may be (1) an incompetence of the femoral valve rarely on a congenital basis usually as a result of a femoral thrombosis with stenosis and regurgitation (2) incompetence of saphenous valves often hereditary and aggravated by postural strain or trauma (3) incompetence of the valves of the communicating veins usually due to increased pressure in the deep veins following iliofemoral thrombosis and sometimes to trauma or phlebitis in the muscle veins.

ment in the majority of cases is desirable as the muscular contractions favor emptying of the venous pools and when supported by elastic compression pain and edema rapidly subside. Prolonged immobilization of patients suffering from varicose veins increases the percentage of deep venous thrombosis or embolism. It is for this reason that patients under

going surgical procedures or expecting delivery have a slightly but definitely higher incidence of thromboses and benefit by a preliminary obliteration of the superficial venous dilatations.

The rational treatment of varicose veins is a complete and if possible permanent obliteration of the varicosities. Of the many procedures practiced throughout the centuries some methods have been discarded some have been revived and some undergo continuous modification. This discussion will be limited to methods developed and practiced in my clinic during the past 12 years.

With the help of the above described circulatory tests of Trendelenburg and Perthes one must obtain an insight into the valvular defects of the venous network (Fig. 13). The diagram illustrates that fundamentally a valvular defect may exist (1) in the femoral valves proximal to the saphenofemoral junction (2) in the valves of the saphenous system either the external or internal saphenous vein and (3) in the communicating veins connecting the superficial and deep venous systems. These three possibilities or their combinations require individual analysis.

Valvular insufficiency of the iliofemoral vein occurs sometimes as a congenital defect but mostly as a result of iliofemoral thrombosis with canalization. This results in a marked rise in pressure in the entire venous system and both saphenous and communicating valves may become incompetent. The treatment of this variety is obviously difficult and can only consist of closing and protecting the superficial and communicating veins from the overflow. A ligation of the iliofemoral vein to prevent reflux from above would only tend to increase venous pressure from below and does not seem indicated. It should be mentioned however that when the femoral vein is ligated in patients with femoral thrombosis to prevent attacks of pulmonary embolism the resulting edema is surprisingly mild and not permanent.¹²

The typical varicose vein is the result of valvular incompetence of the saphenous veins. The major or internal saphenous vein is most frequently involved and while it may be visible only below the knee, careful palpation in the standing position can follow it upward on the thigh to the groin. This palpation is facilitated by percussing the vein gently below the knee and feeling for the percussion wave at the groin. Coughing will also elicit an impulse at the saphenofemoral junction but if

coughing results in a hugh thrill such as one obtains in an arteriovenous aneurysm, then the femoral vein is likely to be incompetent.

The valvular incompetence of the saphenous vein, elicited in the upper third of the thigh, calls for a high saphenous ligation. When my associates and I first started to perform this on ambulatory patients,¹³

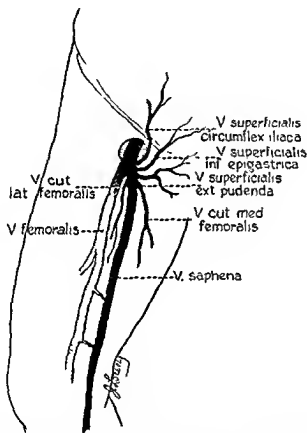


FIGURE 14 The tributaries of the saphenous vein at the saphenofemoral junction. Note that there are two veins emptying from above, two from below and one from the medial side. This pattern is not always encountered as there are considerable variations, but it is well to look for it.

not enough stress was laid on the importance of tying the vein and a number of tributaries entering the vein at the saphenofemoral junction. A diagram illustrates a pattern encountered in classroom dissections by Edwards.¹⁴ It is well to remember as he points out that some of the veins, especially the proximal two, may enter the femoral vein and that the superficial femoral veins may join the saphenous vein at different levels. It is obvious that if ligation is carried out below these tributaries, recurrence may occur through them; therefore, an attempt is made to

expose the saphenofemoral junction and tie all tributaries visible at that level. Diagrams made of the patterns encountered have convinced me that the distribution shown in Fig. 14 is not fully encountered in more than 25 per cent. It is well to keep in mind, however, that two proximal, two distal and one medial tributary may be present.

The ligation of the lesser saphenous, in agreement with the experience of Edwards,¹⁴ has not been necessary in any of our cases. This vein runs beneath the deep fascia for some distance before it enters the deep vein and, furthermore, the popliteal and femoral veins have about six to ten valves above the entry of the lesser saphenous vein. Thus sudden rises of venous pressure, which so readily affect the termination of the great saphenous vein, are readily dampened at this location.

The valvular incompetence of the communicating veins of the thigh have had special emphasis by the work of Ochsner and Mahorner.⁷ They pointed to the frequent leaks between the saphenous and femoral veins on the thigh and demonstrated, by modifying the Perthes test and placing a tourniquet at different levels, that in 33.3 per cent of all their cases, the communicating veins of the thigh had incompetent valves. Of 200 vein ligations performed in the last two years, these leaks have been recognized by us 51 times, roughly in one fourth of the cases, and a low ligation just above the knee was added to the high saphenous ligation. This second ligation as suggested by Mahorner and Ochsner was done not ten days to three weeks after the first one, but simultaneously with the high one.

The operation is done with small transverse incisions under local anesthesia and the patient is either not hospitalized or kept in the hospital only for 24 hours. Descending thrombosis between the two ligatures or below the knee occurs in approximately 20 per cent of the cases. No sclerosing solutions are injected into the vein at the time of operation.

The valvular incompetence of the communicating veins below the knee has been studied recently by Linton.⁸ He described three incisions through which all of the communicating veins could be ligated under the deep fascia and found that the medial group of veins was most commonly involved. While he reported 50 operations, in my material there has been not more than five per cent of all cases in which this extensive operation seemed indicated. It is a new and important contribution and will probably replace the radical excision of veins, which

our clinic has done since 1926 in such intractable cases where the continuous spilling over from the deep veins prevented any firm and permanent closure of varicosities below the knee. There seems to be no harm in trying injections before the subfascial ligations are done. When the main valvular defects are thus eliminated by preliminary ligations of the greater saphenous vein or its communications sclerosing injections must follow to obliterate the dilated segments. These injections

TABLE IV
CONTRAINDICATIONS TO THE INJECTION TREATMENT OF
VARICOSE VEINS

A SYSTEMIC DISEASES

- Angina Pectoris* History of attacks is important
Hyperthyroidism Acute thyroid crisis may be precipitated
Active Tuberculosis Slight pulmonary changes may flare up after the use of tissue irritants
Acute Glands Infections These conditions may be seen in office patients and may be overlooked or neglected. Injections may be followed by phlebitis

B LOCAL CONDITIONS

- 1 *Impairment of Arterial Circulation*
- 2 *Lack of Patency in the Deep Veins* Test of Perthes
- 3 *Thrombophlebitic Edema* with a history of deep phlebitis
- 4 *Acute or Subsiding Superficial Phlebitis* Latent infection may persist for years and may become active following injection. The activity of the latter two conditions may be gaged by the sedimentation rate

(American Medical Assoc. Varicose Vein Bulletin)

given alone, without the support of preliminary ligatures promptly produce a well adherent rapidly organizing thrombus but this thrombus recanalizes unless the back pressure from the deep veins is relieved by ligatures. With the exception of a few authors^{15 16} the principle of preliminary ligation has become widely accepted.

Some authors inject the distal stump of the severed vein, but we prefer to wait a week or ten days after vein ligation. As pointed out before there is a latent infection present so frequently that a spontaneous

thrombosis readily takes place in a number of patients and may make simultaneous injections unnecessary and even uncomfortable.

Injections are started into the highest palpable varicosities and preferably in the horizontal position. Should the veins be collapsed, a blood pressure cuff pumped up to 60 mm. of mercury or a rubber tourniquet, is placed proximally to the site of injection. This procedure readily distends the varicosities. I prefer solutions that may be given with a hypodermic needle and syringe and need no special equipment. In a table prepared for the varicose vein exhibit of the American Medical Association, we have listed the most frequently used solutions, their dosage and their advantages or disadvantages (Table V). At present the five per cent potassium oleate solution is my choice; when a more intense action is required, as in large varices with a scarred intima or saccular varices, behind which an incompetent communicating valve is hiding, a ten per cent concentration is used. In small thin walled veins, or "spider bursts," 50 per cent dextrose is the most harmless and least irritating.

These injections are given twice a week, three or four veins being injected at a time. The cramping with the oleates is minimal. Untoward symptoms consist of pain at the site of injection due to perivenous infiltration, drug sensitivity, especially seen after quinine solutions but not so infrequently after sodium morrhuate and finally a vasovagal syncope, occurring in certain individuals when injected in the standing position. Of the late reactions one must mention the possibility of sloughs which follow faulty technic, but occasionally may occur several inches distally from the site of injection as a result of leakage through thin walled, cutaneous varices. Skin necrosis is especially to be watched for above bony prominences where the skin is tight. Hematomas are often seen in women with fragile vessels or if the bleeding time is prolonged. Embolism used to be the most feared complication but is far less frequent as after surgical excision, in fact it is less frequent than in nontreated varicose veins.

An analysis of the reported cases of pulmonary embolism, including two personal observations, reveals the fact that it invariably occurs in the presence of activated infection or when for any reason prolonged immobilization becomes necessary. A study of the histologic effects of these irritating solutions reveals that the endothelial injury results very

TABLE V

TYPE AND AMOUNT OF SOLUTIONS USED FOR INJECTING VARICOSE VEINS

<i>Solution</i>	<i>Maximal Amount at One Injection cc</i>	<i>Advantages</i>	<i>Disadvantages</i>	<i>Indications for Use</i>
1 15 to 20% sodium chloride	10	Nontoxic prompt action	Marked cramping danger of necrosis	In large thick veins preferable in combination with dextrose
2 50% dextrose	20	Nontoxic slight danger of slough slight cramping	Not irritating enough for larger veins	For smaller thin walled veins
3 30% sodium chloride and 50% dextrose equal parts	10	Nontoxic prompt action	Marked cramping necrosis only if large amounts are injected besides the vein	Most universally useful combines the advantages and reduces the disadvantages of solutions 1 and 2
4 50 to 75% invert sugar	10	Nontoxic slight cramping	Too viscous needs large needles causes marked perivenous edema	May be used instead of dextrose
5 20% sodium chloride 60% invert sugar 1% benzol carbinol	10	Nontoxic slight cramping	Not very active	Generally useful
6 20 to 40% sodium salicylate	5	Prompt action	Very painful danger of necrosis salicylism	Generally useful with caution
7 10% quinine with urethane	2	Prompt action rapid cure painless	Cinchonism anaphylactoid reactions danger of necrosis	Resistant varices test for individual susceptibility
8 5 to 10% sodium morrhuate	1	Nontoxic rapid action slight danger of slough	Marked cramping and peripheralitis Sensitization	Generally useful test for susceptibility
9 5 to 10% potassium oleate	2	Nontoxic a stable compound	Very occasional sensitization	All varices except small thin walled veins

(American Medical Assoc. Varicose Vein Bulletin)

quickly in a fixed thrombus (Fig 15). Only if an ascending red thrombus is superimposed on this and if the dilated sphenous vein is wide open toward the femoral vein, is embolism to be feared. Thus the preliminary ligation adds a safeguard against embolism and only by mobilization of a thrombus in a muscle vein could an infarct be produced. In over 1000

ambulatory vein ligations performed by my associates or myself only two cases of clinically recognized embolism occurred. However, no such procedure can ever be entirely devoid of this danger. Keeping the patient ambulatory and making the stump of the saphenous vein as short as possible are added safeguards. If one were to condemn a method for a possible incidence of embolism, fractures could not be splinted and hernias could not be repaired.

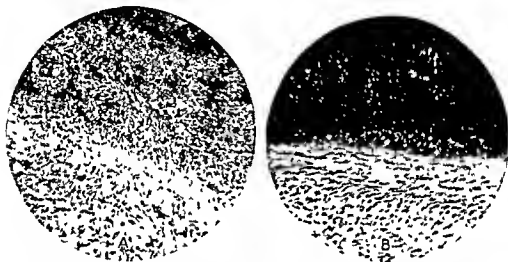


FIGURE 15 A, Section of the wall of a vein one week after the injection of a 50 per cent dextrose. The intima is destroyed. There is an active organization of the clot as compared with B which is an old blind thrombus of the iliac vein. In spite of the age of the thrombus as shown by the intimal scar, there is no tendency to organize the clot (de Takáts, Surg. Gynec. and Obst.)

When adequate follow up records are kept and the patient seen every three months for several years, the percentage of recurrences is quite large in the absence of vein ligations. Although their series is small, Ociskner and Mahorney have published the most enlightening figures on the comparative value of different procedures. Thus injections alone resulted in 42.5 per cent cure, high saphenous ligations combined with injections gave an 82 per cent recovery, whereas a low saphenous ligation resulted in a 50 per cent cure.

The greatest difficulty is encountered with patients who have had a deep phlebitis and have developed an iliofemoral and communicating valvular insufficiency. As early as 1930, we advocated a radical interruption of these communicating veins below the knee.¹³ Whether the new approach of Linton is the answer to the problem is too early to say.

The management of the complications of varicose veins should start by treating the varicose veins in the same manner as though the complications did not exist. In addition ringworm infections are painted with antiseptic dyes. Weeping and dry eczema may require dermatologic consultations. Acutely inflamed ulcers are immobilized with hot boric dressings for a few days. If the ulcer is surrounded by a hard indurated mass it is best to excise it together with the underlying fascia. Pinch grafts or split grafts are applied a few days later to cover the defect. Painful ulcers may be desensitized by crushing their sensory nerve with a hemostat which provides for an anesthesia of several months duration without motor involvement, using the method that Smithwick and White have advocated in arterial diseases.¹⁷ Finally extensive use is made of the gelatin casts of Unna which constitute when properly applied the most satisfactory dressing for all leg ulcers.

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CHAPTER LXII

PATHOGENESIS AND TREATMENT OF EDEMA

By EUGEN M. LANDIS M.D.

Introduction Edema is said to be present when the tissues contain grossly abnormal amounts of fluid. With rare exceptions these collections of fluid are intercellular, distending conspicuously tissue spaces which normally are entirely collapsed or contain only minute amounts of tissue fluid. Edema may be local or general. As examples of local edema the urticarial wheal, the swelling of inflammation, and the periorbital swelling of trichinosis arise from abnormalities of fluid balance in restricted areas. The present chapter, however, deals primarily with the generalized forms of edema in which the disturbance of fluid balance is widespread. In mild cases edema may be grossly obvious only in the subcutaneous tissues of the ankles or face, but in severe cases the subcutaneous tissues of the entire body are markedly involved, often with extension to some or all of the serous cavities. These generalized forms may be subdivided clinically into cardiac edema, nephrotic edema, and that form which though still termed nephritic edema is now believed to be due to widespread abnormality of the capillary blood vessels.

Clinically edema is identified by pitting on pressure, but this is a relatively crude test since limb volume and body weight must be greater than normal by ten per cent before pitting can be demonstrated definitely. Finer methods of examination will detect fluid retention of milder grades termed preedema or abortive edema, in which the volume of tissue fluid is greater than normal but still not great enough to permit pitting on pressure.

This gradual transition from normal fluid distribution to gross clinical edema suggests that the pathogenesis and treatment of edema should be described in terms of those factors which normally control (a) the total amount of body fluid, (b) the movement of fluid to and fro between the tissue spaces and the circulating blood, and (c) the distribution of fluid between various portions of the body.

I FACTORS CONCERNED IN THE NORMAL DISTRIBUTION OF BODY FLUIDS

The occurrence of edema recognized as an outstanding medical problem even before the time of Galen led to the proposal of many hypotheses concerning the mechanism which controls the transportation and distribution of body fluids. It was recognized quite early that in normal individuals the volume of tissue fluid suffers only transitory and small changes despite wide variations in water intake, activity and posture. On the other hand, if there is some tendency toward edema formation the copious ingestion of water usually increases the normally meager amount of tissue fluid until clinical edema appears. These patients suffer apparently from a more or less serious breakdown of the normal mechanism of fluid transport.

Starling¹ in 1896 advanced the first reasonably complete hypothesis explaining the mechanism by which equilibrium is maintained between blood and tissue fluid under diverse conditions. The essential parts of this hypothesis can be summarized under four heads: (a) The blood flows through the capillary network under pressure which if unopposed filters fluid from the blood plasma through the capillary wall into the tissue spaces. (b) The capillary wall though permeable to water, salts and simple organic compounds is in most tissues relatively impermeable to the plasma proteins. (c) Those substances (such as salts, urea, creatinine, glucose, etc.) which pass easily through the capillary wall and are present in approximately equal concentration in blood plasma and tissue fluid cannot exert a permanent osmotic pressure across the capillary wall and should not therefore affect the distribution of fluid except temporarily. (d) The plasma proteins by reason of their greater molecular dimensions are retained by the capillary wall and thereby develop a small but physiologically important colloid osmotic (or oncotic) pressure which if unopposed leads to absorption of fluid from the tissue spaces.

According to Starling therefore the constancy of blood volume and tissue fluid volume depends primarily upon the balance between capillary blood pressure and the osmotic pressure of the plasma proteins both acting in association with a capillary wall which is relatively impermeable to protein. This ingenious hypothesis though theoretically sound was for many years open to considerable criticism owing to the difficulties

surrounding direct measurements of capillary blood pressure and of the colloid osmotic pressure of the blood plasma. Recent work has however indicated the fundamental validity of this concept.

Epstein² in 1917 called attention to the relation between nephrotic edema and lowered concentration of the plasma proteins. War edema was also found to be associated with hypoproteinemia.³ It was observed that the edema disappeared as soon as adequate protein intake restored the normal concentration of the plasma proteins.^{2, 3} That the colloid osmotic pressure of the plasma was reduced in some types of edema was definitely established by Krogh,⁴ Schade,⁵ Gowers,⁶ Meyer,⁷ and others. It became evident, however, that in other types of edema the plasma protein percentage was within normal limits.

During this same period Krogh⁴ and Lewis⁸ showed conclusively that the capillary vessels are themselves independently contractile and that they are capable of responding individually in a delicate manner to the circulatory needs of the immediately adjacent tissues. However the circulating blood is still separated from the tissue spaces by a single layer of endothelial cells which form the walls of the capillary vessels. It is to be expected that the properties of this membrane will affect the movement and distribution of body fluids.⁹

The observations of Krogh indicated that the capillary walls collectively offer a tremendous surface for diffusion and fluid movement since their total area in the human being amounts to at least 6300 square meters. Chemical¹⁰ and physiological¹¹ studies agreed in showing also that the capillary endothelium behaves like a passive (*i. e.*, nonsecreting) filtering membrane. It permits water, salts and simple organic compounds of small molecular size to pass rapidly but under ordinary conditions retains the plasma proteins as well as certain foreign colloidal substances which are composed of large molecules. This relative impermeability to protein is lost, however, with injury of any kind as will be described below.

Direct cannulation of single capillaries has also shown^{9, 11, 12} that in the arteriolar portion of the capillary network average blood pressure is greater than the colloid osmotic pressure of the plasma proteins. On the contrary, in the venous portion of the capillary network average blood pressure is less than the colloid osmotic pressure of the plasma proteins. Thus these two forces are actually balanced so that on the

average such filtration as takes place in the arteriolar portions of the capillary bed is balanced by absorption in the venous capillaries and minute venules 11 Figure 1*A* illustrates this relationship diagrammatically

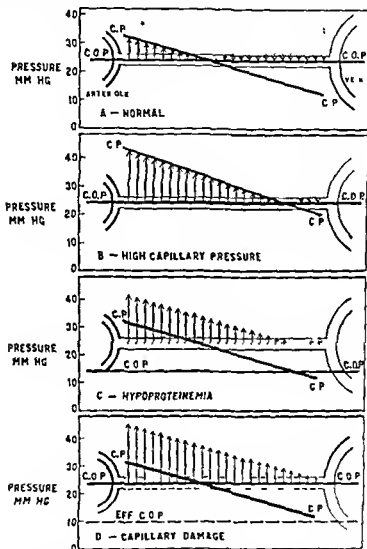


FIGURE 1 Diagram illustrating filtration and absorption in relation to capillary blood pressure and the colloid osmotic pressure of the plasma proteins *A* Normal conditions with balance between filtration shown by upward arrows and absorption shown by downward arrows *B* Increased filtration due to high capillary blood pressure *C* Increased filtration due to lowered colloid osmotic pressure *D* Increased filtration due to capillary damage which by permitting leakage of protein reduces the effective colloid osmotic pressure of the blood

cally Supported by chemical and physiological evidence, the Starling hypothesis forms a logical basis for classifying the factors responsible for edema

II. FACTORS IN THE PATHOGENESIS OF EDEMA

The known physical factors which favor the production of edema are listed to the left in Table I. Those factors which are designated "primary"

TABLE I

<i>Factors Favoring Edema Formation</i>	<i>Clinical Examples</i>
A PRIMARY	
1 Elevated capillary pressure	1 (a) Venous compression (b) Thrombophlebitis (c) Cardiac edema with venous congestion
2 Lowered colloid osmotic pressure	2 (a) Nutritional edema (b) Nephrotic edema (c) Cardiac edema late stages with malnutrition
3 Damage to capillary wall	3 (a) Inflammatory edema (b) Nephrotic edema (c) Cardiac edema (?), chronic anoxemia
4 Lymphatic obstruction	4 (a) Lymphedema (b) Cardiac edema with venous congestion
B CONTRIBUTORY	
5 Low tissue pressure	5 Edema of periorbital tissues and genitalia
6 High NaCl intake	6 Increases edema if water is available
7 High fluid intake	7 Increases edema if NaCl is available
8 Warm environment	8 (a) Heat edema (b) Increases all types of edema
9 Disturbed innervation	9 (a) Tropho-edema (b) Unilateral edema in hemiplegia
10 Miscellaneous	10 Vitamin B ₁ deficiency (?) Hormonal abnormalities (?)

are fundamentally important since each one, in sufficient grade, can by itself produce edema. In addition, however, certain other influences, which do not ordinarily produce edema of themselves, can modify the severity of, or change the distribution of, edema produced by one or more of the primary causes. These have been named "contributory factors" because of their secondary importance. To the right in Table I are shown clinical

examples in which these forces primary or contributory are frequently observed. From the nature of the forces involved and their opposite action it is to be expected that edema can be due (a) to gross abnormalities of certain single factors or (b) to the combined effect of several factors acting together.

1. Capillary pressure, owing to conspicuous spontaneous variation can be described by absolute figures only when large numbers of direct determinations are averaged under standard conditions. With this reservation average human capillary pressure at heart level can be said to be about 32 mm. of Hg in the arteriolar capillaries and 19 mm. of Hg in the venous capillaries.¹² Capillary pressure is increased in the normal subject (a) by arteriolar dilatation from local heating inflammation or the accumulation of tissue metabolites and (b) by the elevated venous pressure which is produced by lowering an extremity below heart level. Under these conditions filtration predominates and absorption is diminished.

On the contrary local chilling or raising an extremity above heart level diminishes capillary pressure so that filtration is difficult and absorption predominates. In spite of these physiological fluctuations of capillary pressure and fluid movement the normal subject fails to develop clinical edema because the imbalance is transient the movement of fluid is limited and the temporary distortion of fluid balance is corrected by greater movement of lymph so that the volume of tissue fluid though measurably increased does not become dangerously large.

Of greater clinical importance are the *persistent* elevations of capillary pressure which by reason of their duration disturb fluid balance to the extent of producing clinical edema. Whenever venous pressure is continuously elevated (Fig. 1 B) by a tight bandage by the internal obstruction of thrombophlebitis or by the external pressure of a neoplasm filtration is increased and if the imbalance persists long enough edema appears. As would be expected if the veins and lymphatic vessels are both blocked the edema appears earlier and is more conspicuous. In ambulatory patients most forms of edema tend to appear first in the region of the ankles because the added hydrostatic pressure of the blood in the vertically placed veins accentuates the tendency for fluid accumulation in dependent tissues. When the patient is confined to bed the horizontal position eliminates this hydrostatic disadvantage and the

ankles quickly become less edematous as the fluid moves to the sacral region, the face, or the body cavities. This same hydrostatic element is responsible for the greater edema of one side of the body, which is frequently observed when a grossly edematous patient lies in one position for prolonged periods. Increased venous pressure is also an important factor in the edema that accompanies congestive heart failure.

In clinical conditions it is safe to assume that capillary pressure is abnormally high whenever venous pressure is above normal. Beyond this our knowledge of capillary pressure in disease is meager. The various indirect or capsular methods furnish very diverse results which are open to criticism on technical grounds. Direct measurements by cannulation of single capillaries have provided considerable information concerning normal capillary pressure and its variations. This accurate, but technically laborious, method is difficult to apply to clinical problems because the great normal variability of capillary blood pressure requires that large numbers of single readings must be averaged if significant values are to be obtained.

2. Hypoproteinemia and Reduced Colloid Osmotic Pressure of the Blood Plasma: The plasma protein percentage is normally fairly constant, ranging from 6.5 to 8.0 Gm per cent, of which globulin forms from 1.2 to 3.0 Gm. per cent and albumin from 1.6 to 5.0 Gm per cent. The colloid osmotic pressure of the plasma proteins, determined directly in a suitable osmometer or calculated from chemical analyses of total protein and albumin,¹³ ranges normally from 21 to 26 mm. of Hg with an average of 24 mm. of Hg. Under normal conditions, fluctuations in the concentration of plasma proteins, and therefore in the colloid osmotic pressure of the blood, are small. Plethysmographic studies in normal subjects indicate that even these small fluctuations affect fluid movement as would be expected from the Starling hypothesis, but the changes in tissue volume are not great enough to be visible or even detectable by ordinary clinical methods.¹⁴ In experimental animals, however, gross hypoproteinemia has been produced (a) by plasmapheresis,¹⁵ and (b) by protein starvation. Clinically detectable edema develops in these animals when the plasma protein percentage is reduced to 1.0 Gm. per cent or less, and persists as long as this hypoproteinemia is maintained.

In patients hypoproteinemia is responsible for the edema associated with prolonged protein starvation and with the nephrotic syndrome. In these two conditions slight edema is usually found in ambulatory patients when the total plasma protein percentage is less than 5.5 Gm per cent and when the colloid osmotic pressure of the plasma is less than 17 mm of Hg. Definite edema is practically always present in *untreated* patients if the plasma proteins are below 4.5 Gm per cent.¹⁰ The concentration of albumin is more important than that of globulin and total protein because the albumin molecules being smaller are osmotically more active and are chiefly responsible for the colloid osmotic pressure of the plasma. The plasma albumin is reduced most conspicuously in the nephrotic syndrome and the colloid osmotic pressure of the blood can be as low as 8 mm of Hg or only one third its normal level. Under these conditions capillary pressure is largely unopposed and filtration is correspondingly great (Fig. 1 C). In mild nutritional edema the protein deficit arises either from proportional reduction of albumin and globulin or more usually from excessive reduction of albumin. In advanced cardiac disease with prolonged malnutrition mild grades of hypoproteinemia due to voluntary restriction of diet are often associated with moderate venous congestion, the resulting edema being of mixed etiology.

3 Permeability of the Capillary Wall In the human extremity under normal conditions the capillary walls are approximately 99 per cent efficient in preventing the passage of plasma proteins.¹¹ Impermeability to proteins is not absolute but is so nearly complete that the conditions required by the Starling hypothesis are fulfilled for all practical purposes. Thus in discussing the pathogenesis of peripheral edema estimations of the colloid osmotic pressure of blood plasma made *in vitro* against a totally protein tight collodion membrane can be used justifiably to express the effective colloid osmotic pressure of the blood against a normally protein tight capillary wall. This is not true however if the permeability of the capillary wall has been increased by injury. Normal capillary filtrate according to indirect evidence contains protein in concentrations of 0.3 per cent or less. Similarly edema fluid produced mechanically under conditions in which capillary permeability is still relatively normal generally contains from 0.01 to 0.4 per cent protein.

Whenever tissue fluid accumulates in excessive amounts it passes promptly into the lymphatic vessels from which it can be collected as

lymph With certain precautions the protein content of this lymph can be used to estimate the protein content of tissue fluid and therefore the grade of capillary impermeability with respect to protein Drinker¹⁵ found that in the extremity lymph produced by mild venous congestion contains as little as 0.25 per cent protein whereas lymph from exercising muscle usually contains 1.0 per cent protein This suggests that muscular activity increases capillary permeability slightly Earlier studies showed also that hepatic and intestinal capillaries are more permeable than those of the extremities Under normal conditions however the lymphatic system rapidly carries away the surplus tissue fluid and clinical edema does not occur

Gross injury of any type increases the permeability of the capillary wall so that the plasma proteins pass very easily and the filtration of fluid is increased to as much as nine times the normal rate¹¹⁻¹⁷ When the plasma proteins pass through the capillary wall they cannot contribute to the colloid osmotic pressure of the blood plasma and capillary pressure is no longer opposed in the area of injury Therefore filtration is much increased while absorption is diminished or absent (Fig. 1 D) Burns severe inflammation or chemical injury lead to local edema the fluid of which contains as much as five or six per cent protein due to increased capillary permeability It is obvious that generalized edema cannot be due to gross capillary damage of this magnitude throughout the entire body for if this were the case a shocklike state would be produced great loss of plasma would almost immediately reduce blood volume to the point at which continued circulation would be impossible

Of more importance in the pathogenesis of general edema are the milder forms of generalized increase of capillary permeability which do not produce shock but still affect fluid balance slightly over long periods of time Combined congestion and anoxemia lead to the filtration of relatively large volumes of fluid containing as much as one or two per cent protein The protein content of edema fluid from cardiac patients is often above 0.5 per cent and it has been suggested that widespread mild injury of the capillary wall by continued anoxemia may play a role in cardiac edema It has also been found that edema fluid from patients with acute diffuse glomerulonephritis often contains protein in excess of one per cent indicating slight injury of the capillary endothelium However the protein content of edema fluid varies widely and

further study will be required before it can be concluded definitely that increased capillary permeability is primarily responsible for these two types of edema

4 Lymphatic Drainage The lymphatic capillaries penetrate widely into the tissue spaces with walls that offer only slight obstruction to the passage of water, dissolved salts and such proteins or particulate matter as may have found their way into the tissue fluid¹⁸ Excessive tissue fluid passes rapidly into the lymphatic capillaries from which as lymph it is pushed along the larger lymph vessels chiefly by muscular movement aided by valves in the larger lymphatic trunks During rest when absorption of fluid by way of the capillaries is active the volume of tissue fluid and therefore of lymph is small samples can be collected only after vigorous massage of the tissues During muscular activity or during mild venous congestion capillary reabsorption is diminished and the flow of lymph increases conspicuously The lymphatic system thus protects the tissues against the accumulation of abnormal amounts of tissue fluid by returning to the blood stream both excess fluid and such proteins as it may contain

When the lymph vessels are underdeveloped as they may be congenitally or when they are obstructed by lymphangitis or external pressure edema appears merely because the lymphatic system is unable to cope with the physiological amount of tissue fluid that accumulates as a result of postural changes or activity Edema of the extremities which is due to dysfunction of the lymphatic system itself is termed lymphedema

The large lymphatic trunks empty into the venous system at the base of the neck If venous pressure is elevated by cardiac decompensation the contents of the thoracic duct meet abnormal resistance and the flow of lymph into the veins of the neck is impeded This is frequently cited as one of the factors responsible for the edema of congestive heart failure

5 Tissue Pressure The volume of the tissue spaces normally available for extravascular fluid is limited As extravascular fluid collects in the tissue spaces the tissue elements must be separated to accommodate the additional fluid This distention develops a tissue pressure which neutralizes capillary pressure and opposes further filtration¹⁹ Under normal conditions tissue pressure helps to prevent excessive filtration and assists in maintaining normal blood volume against considerable hydrostatic disadvantage Thus in standing normal subjects fail to develop

edema in dependent tissues because tissue pressure reduces the rate of filtration long before limb volume has increased by the ten per cent which is required to produce pitting edema.

The mere existence of edema however shows that this power of the tissues to resist fluid accumulation is distinctly limited. Direct measurement of tissue pressure indicates that when a tendency toward excessive filtration persists over long periods of time the protective action of tissue pressure becomes less presumably because the tissues are gradually stretched. Yet looseness of the tissues cannot be the primary cause for the appearance of any edema since the relaxed abdominal skin of multiparae or the loose orbital tissues are not edematous unless one of the primary causes of edema formation is present. However if physical conditions favor excessive filtration over long periods the loosely constructed tissues will show pitting edema before the more compactly constructed tissues. Therefore nephritic and nephrotic edema may produce swelling of the face periorbital tissues and genitalia before other regions are grossly edematous.

6 Sodium Chloride Intake The excessive ingestion of sodium chloride by the normal individual leads to thirst increased ingestion of water transient slight increase in body weight followed by rapid excretion in the urine of both the additional salt and water without the development of edema. However given one of the primary factors favoring edema formation fluid will accumulate more freely if salts are available for the elaboration of a fluid having the native composition of tissue fluid itself. The excessive ingestion of sodium chloride and water therefore accentuates existing edema or makes latent edema grossly apparent. The urinary excretion of sodium chloride and water is delayed in such patients since the water and salts are diverted to the tissue spaces. This facilitation of fluid retention by salt is common to all forms of edema so that efficient reduction of sodium chloride intake is generally useful in the treatment of any edema. However when venous congestion is extreme or when the plasma proteins are very low even rigid restriction of salt intake will be only partially successful.

It is the sodium ion and not the chloride ion that is responsible for this retention of fluid. In mildly edematous patients edema is increased by the ingestion of sodium chloride sodium bicarbonate or sodium bromide. Chlorides such as potassium chloride ammonium chloride or

calcium chloride do not increase edema and may actually decrease it by inducing diuresis. Available evidence indicates that these salt effects are merely contributory factors in fluid balance and that their action becomes significant only if one of the primary factors is present.

7. **Fluid Intake:** The normal individual can ingest large amounts of fluid without changing appreciably the volume of tissue fluid because excess water is rapidly excreted by the kidneys. In the presence of one of the primary causes of edema, and if salt is available from the diet, excessive ingestion of water accentuates existing edema. A salt poor régime diminishes the amount of water retained even with a high fluid intake. Therefore, in the treatment of edema, restriction of fluids is less necessary if the intake of sodium chloride is rigidly limited. Ordinarily, however, best results are obtained from restricting both fluid and salt.

8. **Heat:** The volume of the extremities increases, immediately and slightly, with local heating or with general body warming. In large part this immediate increase in volume is due to vasodilatation and increased vascularity of the skin and subcutaneous tissues. Superimposed upon this immediate effect, a slower increase in volume is also observed. The latter is due to increased filtration produced by peripheral vasodilatation, elevation of capillary blood pressure, and increased endothelial surface available for filtration. Normal individuals are able to adjust for the changed blood flow of peripheral vasodilatation without the appearance of gross edema. Under exceptional circumstances, as in the tropics, edema of the ankles may be observed although no cardiac or renal abnormality can be detected.²⁰ Even in temperate climates patients with latent or slight edema usually observe that their edema is more pronounced in warm weather.

9. **Disturbed Innervation:** It was mentioned above that lymph is propelled passively along the larger lymph vessels in large part by contraction of skeletal muscles. Certain disturbances of innervation produce not only peripheral vasodilatation but also paralysis of the skeletal muscles. Thus in cardiac patients, with latent or mild general edema, hemiplegia is followed at times by conspicuous edema of the paralyzed extremity while the opposite extremity is normal or at most slightly edematous.²¹ It has been stated that denervation modifies the permeability of the capillary wall but direct evidence in favor of this view is lacking. In general, the effects of disturbed innervation can be explained more simply by vasodilatation

or by defective drainage of lymph. Local edema of this type is also observed in hysterical paralysis and in poliomyelitis.

10 Certain Less Well-defined Factors During the development of edema oliguria is usual and for this reason edema has often been ascribed to lessened urine formation, to decreased renal excretion of sodium or chloride and to failure of renal excretion of water. This is certainly true in anuria and to a certain extent in advanced renal insufficiency with oliguria. In many cases of edema, however, kidney function *per se* is good; edema has under these conditions been ascribed to so-called pre-renal deviation of water in that fluid is deposited in the tissue spaces and is not presented to the kidney for excretion. The various factors mentioned individually above are special causes of this pre-renal deviation.

Deficiency of vitamin B₁ produces beriberi in which edema is ordinarily associated either with myocardial insufficiency or hypoproteinemias or both. In some cases however mild edema appears even though the plasma proteins and cardiac function are normal. It has been suggested that B₁ vitaminosis increases capillary permeability or increases capillary blood pressure but direct evidence is lacking.

Many hormones are known to affect water or salt metabolism but the evidence so far indicates that they are of importance only in rare and extreme cases having little relation to the common forms of generalized edema. Pituitrin is an antidiuretic leads to water retention but does not produce clinical edema in normal individuals. Occasionally edema is actually reduced by continued administration of pituitrin. That antidiuretic substances are responsible for the edema of the late toxemias of pregnancy has been claimed and also refuted -- The premenstrual retention of fluid observed in many women is occasionally conspicuous enough to produce slight edema which disappears during other portions of the menstrual cycle.²³ Women with mild edema of any type will often observe spontaneously that edema is increased immediately before menses.

Particularly in nephrotic edema so-called spontaneous diuresis is occasionally observed. Without change in the plasma protein percentage large amounts of edema fluid will be discharged by copious diuresis for which there is at present no explanation. The mechanism which produces water diuresis in the normal individual is still a matter of controversy and it is probable that future observations will discover other

factors hormonal or dietary which affect water balance profoundly. It is conceivable that these studies may provide a diuretic substance more physiologic and even more effective than those now available.

SUMMARY

Certain primary abnormalities of the capillary pressure—plasma colloid osmotic pressure—capillary wall system always produce a tendency toward edema which means merely that with ordinary diet fluid intake activity salt intake and renal excretion the patient will exhibit edema whereas a normal individual under the same conditions will not. Clinical experience has shown that the edematous patient can often be relieved of his edema by imposing conditions which prevent fluid accumulation—e g rest in bed limitation of fluid restriction of salt and stimulation of the kidneys by diuretics. In this way the tendency toward edema formation can be nullified by artificial means and the patient will be kept relatively free of edema in spite of persisting cardiac failure hypoproteinemia or capillary damage. This clinical observation has been advanced as evidence that edema cannot be explained by the physical forces described above. Strictly speaking this is not a valid objection since relaxation of the abnormal regimen is again followed by fluid accumulation unless the underlying abnormality of the capillary pressure—plasma colloid osmotic pressure—capillary wall system has been corrected.

Nutritional and nephrotic edemas are uniformly associated with low concentrations of plasma protein and a reduced colloid osmotic pressure of the plasma. Capillary permeability and capillary pressure are not increased; it has in fact been suggested recently that permeability is less than normal. The edema fluid generally contains 0.2 per cent protein or less. Unless modified by treatment the tendency toward edema persists until the plasma proteins are 5.5 per cent or more or until the colloid osmotic pressure of the blood exceeds 17 mm of Hg. Occasionally a copious diuresis occurs even in the presence of marked hypoproteinemia.

Nephritic and inflammatory edemas are generally ascribed to injury of the capillary wall and increased permeability. In true nephritic edema occurring in an initial attack of acute diffuse glomerulonephritis the edema fluid may contain as much as 1.0 per cent protein indicating

slight but definite damage of the capillary wall. Oliguria if intense may also be partially responsible for the formation of edema. In marked inflammatory reactions e. g. burns or local infections edema fluid may contain as much as five or six per cent protein. Capillary pressure is elevated but apparently increased capillary permeability is the more important factor.

Cardiac edema is far more complicated in its pathogenesis. In acute congestive failure edema is ascribed chiefly to high capillary pressure resulting from venous congestion. Retarded lymph drainage and anoxemia may play a part also. Protracted cardiac decompensation leads to restricted intake of food and finally to malnutrition with moderate hypoproteinemia which in conjunction with venous congestion often makes the late stages of cardiac edema extraordinarily difficult to treat effectively.

III. TREATMENT

The ultimate purpose of treatment is to restore normal volume and distribution of tissue fluid. Hence therapy is directed toward (a) correction of any abnormality of the capillary pressure—colloid osmotic pressure—capillary wall system and (b) if such direct attack is impossible the proper use of rest, diet, fluid restriction, salt limitation and diuretic drugs to oppose the tendency toward edema formation and to prevent the accumulation of fluid even though the underlying cause for edema persists unchanged. As soon as the underlying elevation of capillary pressure, hypoproteinemia or capillary injury disappear the imposed regimen can be relaxed without return of edema.

1. **General Measures.** *Bed rest* is desirable in all forms of edema since it eliminates the hydrostatic disadvantage of the erect position. Patients with mild edema will frequently respond by diuresis shortly after bed rest is begun but in severe edema the fluid is merely redistributed. Edema of the legs decreases as the fluid shifts to other parts of the body. Bed rest is most valuable in cardiac edema since restoration of cardiac efficiency removes the underlying cause of the fluid retention and at the same time improves kidney function. In nephritic edema bed rest helps prevent chilling and speeds the development of spontaneous diuresis. In severe nephrotic edema bed rest is relatively less effective but is generally advisable particularly when diuretics are being used.

Restriction of Salt Intake: The sodium chloride content of the usual dietary varies between 6 and 15 Gm. per day, with large individual differences according to the amount of seasoning added at table. Restriction of dietary sodium and sodium chloride is beneficial in all forms of edema. Restriction may be made moderate or severe, depending upon the grade of edema which is present. For moderate restriction it is sufficient to (a) avoid adding salt to the food at table, and (b) omit salt preserved meats, meat extracts, salty cheese, and salted fish. Rigid salt restriction involves in addition: (c) The use of salt-poor butter and salt poor bread; (d) omission of all salt in the preparation of food, (e) avoidance of bananas, celery, cornmeal, crackers, dates, molasses etc. and finally (g) the cooking of vegetables in several changes of water.

Salt deprivation makes the food less palatable at first, but patients usually become accustomed to lack of seasoning in a few days or weeks. Pronounced anorexia, nausea, weakness, or muscular cramps may be produced by too prolonged or too rigorous salt restriction, particularly in patients who have little or no remaining edema. In patients who complain of these symptoms it is advisable to determine the plasma chlorides in order to recognize hypochloremia.

The use of salt substitutes is not generally satisfactory. The addition of potassium chloride from a shaker can be tried, but the taste is unpleasant to most patients. Many of the commercial salt substitutes contain the sodium salt of an organic acid, e. g., sodium formate, and are undesirable because it is the sodium ion which assists fluid retention. It should be remembered that it is irrational to give large amounts of alkaline waters, sodium bromide, or sodium bicarbonate to patients during salt limitation. The potassium salts are not contraindicated (see page 1815). The use of acid salts as diuretics will be described below.

Restriction of Water Intake: Water balance can be followed most satisfactorily by daily weighing under constant conditions, since sudden fluctuations of body weight are due to changes in the amount of body water, whereas fluctuations due to nutrition occur much more slowly. In addition, the daily fluid intake and urinary output should be measured and recorded. The fluid intake offers only an approximate figure for total water available since it does not include (a) water in the food itself, particularly that of green vegetables and fruits, and (b) water of oxidation arising from metabolism within the body. Urinary output

offers also only an approximation of fluid loss since it does not include (a) evaporation from the lungs (b) insensible and obvious perspiration and (c) fecal water. Vomiting, diarrhea, dyspnea or excessive perspiration tend to increase total water loss. Thus the intake and output chart is most useful in measuring the immediate effectiveness of diuretic agents while body weight provides a better measure of changes in total fluid balance.

The degree of fluid restriction recommended must take into account (a) the amount of edema (b) the functional capacity of the kidneys and (c) the degree of nitrogen retention or acidosis. If the concentrating power of the kidneys is impaired and if the blood urea nitrogen is elevated fluid restriction should be less rigorous. In these patients rigid salt restriction associated with more liberal fluid allowance is preferable to moderate restriction of both fluid and salt.

Obviously in massive edema if urea clearance is normal rigid restriction of fluid to as little as 600 cc per 24 hours is safe. Usually however limitation to 1000 cc per 24 hours is sufficient and can be continued for long periods without excessive discomfort. Edematous patients suffer little from thirst unless accustomed to a large fluid intake. Habituation to smaller fluid allowance then requires several days.

In severe acute diffuse glomerulonephritis Volhard recommends complete abstinence from water for two or three days but this rigorous regime is not indicated in other conditions or even in mild glomerulonephritis. All patients with edema do well however with a dry day consisting of complete restriction of fluid for 24 hours about once weekly. This is often followed for one or two days by a slight but definite diuresis. In general it is best to attempt to keep fluid intake equal to or slightly below urinary output since this produces a negative water balance owing to the extraneous water loss mentioned above.

When diuresis has once begun fluid restriction can be relaxed. A sudden high fluid intake e.g. 1500 cc in one hour will occasionally begin a so-called flood diuresis which will eventually rid the body of large amounts of edema fluid before ceasing.

Diet in edema should with a few exceptions be adequate in protein high in calories rich in vitamins and low in salt. In treating the edema of severe acute glomerulonephritis Volhard recommends complete starvation for two to five days since hypertensive encephalopathy is lessened and spontaneous diuresis is hastened by this procedure. This is feasible

in well nourished individuals but must be qualified for the weak and for those with mild glomerulonephritis. Ordinarily small amounts of sweetened tea and fruit juices can be given for two days followed thereafter by soft carbohydrate foods along with fluids in a volume equivalent to the previous days urinary excretion. As soon as diuresis appears diet and fluid intake can be returned gradually to normal.

Protein intake should be restricted only for brief periods and for definite indications: *i.e.* (a) to diminish the excretory work of the kidneys in serious acute diffuse glomerulonephritis until spontaneous diuresis appears and (b) in any form of edema when the blood urea nitrogen is rising rapidly. Except for these situations protein intake should be at least 1 Gm per kilo per day since it is undesirable to restrict proteins for prolonged periods. The lay dictum of "no meat in kidney disease or dropsy" is pernicious since prolonged protein restriction does no good and probably predisposes to the development of the nephrotic syndrome.

When the plasma proteins are low as in nephrotic edema or in some cases of chronic cardiac edema protein intake is kept as high as appetite and gastrointestinal tolerance will permit—usually between 100 and 150 Gm per day exceptionally even 200 Gm. It must be admitted that a high protein diet does not influence hypoproteinemia in any striking manner but over prolonged periods recovery seems to be hastened. The diet should also be high in carbohydrate since a positive nitrogen balance is obtained more easily with a high general caloric intake. When hypoproteinemic edema and azotemia occur together it is necessary to adopt a middle course with respect to dietary protein.

Alkaline and acid ash diets have each been advocated for the treatment of edema. The latter can be used logically as an adjuvant measure in prescribing acid salts as diuretics.

2 Diuretic Drugs Diuretics are administered for the purpose of stimulating the kidneys to excrete water and salt more rapidly than they would spontaneously. In the normal individual the kidney responds very promptly to increased body water by a diuresis but in the edematous patient this physiologic response is in abeyance. In many instances however appropriate drugs will stimulate the kidneys to activity and this artificial diuresis relieves the edema at least temporarily. As might be expected the efficiency of diuretics is greater when (a) renal function

per se is good (b) edema is mild and (c) when the underlying abnormality of cardiac function capillary pressure, or colloid osmotic pressure is being corrected simultaneously

Diuretics are *contraindicated*, in treating the truly nephritic edema of acute diffuse glomerulonephritis since additional stimulation of the damaged kidneys is useless and often injurious. Proper restriction of salt diet and fluid intake with bed rest are usually sufficient to bring on spontaneous diuresis

Diuretics are also often useless in cardiac edema associated with advanced renal insufficiency since the few remaining renal units are already stimulated maximally by retained urea or fixed acids. In nephrotic edema the ordinary diuretics are often ineffective if the plasma proteins are below 4 Gm per cent moderately effective if they are between 4 and 5 Gm per cent and usually very helpful when the plasma proteins are over 5 Gm per cent. Many of the milder diuretics are capricious being ineffectual on one trial and effectual later. It is best to try them in series beginning with the more physiological perhaps in the following order until the desired effect is obtained

Urea, in doses of 20 Gm (1 drams) can be given in fruit juice or tea two to four times daily to patients with good kidney function. It produces good results in some cases of nephrotic edema and in many cases of cardiac edema. The artificial rise of blood urea is harmless but in some cases gastrointestinal disturbances thirst slight headache and lassitude may limit dosage. In suitable cases it can be used over prolonged periods for the control if not the complete relief of moderate edema. The administration of urea is *contraindicated* if azotemia is present

Purine Diuretics Theobromine used either as the base or as one of its salts is administered orally in doses of 0.6 to 1.0 Gm (10 to 15 grains) three to five times per day. It is best used over periods of only three or four days since it gradually loses its effect when given continuously for longer periods. Theophyllin or preferably theophyllin ethylenediamine is somewhat more active as a diuretic and is given in doses of 0.1 to 0.2 Gm (1 1/2 to 3 grains) three times a day in hot tea. Gastrointestinal or renal irritation is occasionally observed. Theophyllin ethylenediamine is now available for intravenous administration also

Potassium nitrate chloride or acetate, in doses of 1 Gm (15 grains) 3 to 5 times per day are useful occasionally but not with complete regularity. These salts are not to be given when renal function is impaired since retention makes toxic symptoms such as nausea, vomiting and diarrhea more likely. The potassium salts are more potent when reinforced by a low sodium high potassium diet ²⁴

Acid producing salts are usually administered in the form of ammonium chloride or ammonium nitrate. Doses of 2 Gm (30 grains) are given three to five times daily in enteric coated capsules. In most cases it is essential to determine the plasma CO_2 occasionally to avoid excessive acidosis. Results are generally better in cardiac edema than in severe nephrotic edema. A diet with acid ash can be used to supply part of the acid required ²⁵. The acid producing salts lose their effect and become actually dangerous in the presence of renal insufficiency since retention may produce severe acidosis.

Mercurial Diuretics. Calomel, Guy's Hospital pill and merbaphen (novasurol) have been superseded by more dependable and less toxic organic compounds of mercury. Even the latter are however contraindicated in acute renal disease and in renal insufficiency owing to the greater danger of mercurialism. Mersalyl (salyrgan) produces diuresis by reducing tubular reabsorption of water ²⁶. Mercuparin containing both organic mercury and theophyllin apparently produces diuresis partly by increasing glomerular filtration and partly by decreasing tubular reabsorption of water ²⁷. Both these drugs are given intravenously preferably in the morning in doses of 1 or 2 cc (15 to 30 minims) of ten per cent solution at intervals of three to five days. It is safest to begin with an injection of 0.5 cc (7½ minims) to detect undue sensitivity to mercury. Diuresis begins in two to three hours, reaches its peak in six to ten hours and continues at lower levels for 24 to 48 hours. Careful intramuscular administration can be used but subcutaneous injection is painful and leads to sloughing lesions.

Recently suppositories containing an organic derivative of mercury (mercurin) have become available. After a cleansing enema the suppository is inserted preferably in the morning; the resulting diuresis is less pronounced but lasts longer than that produced by intravenous administration ⁸.

All the mercurial diuretics are more consistently effective if the patient has been started 48 hours before on a course of ammonium chloride or nitrate.²⁹ Urea by mouth may also be combined with the intravenous or rectal administration of mercurial diuretics. Such combinations are more apt to be beneficial than either drug alone.

The completely safe repeated use of mercurial diuretics is limited to patients with cardiac edema and good kidney function as measured by concentrating power or urea clearance. In nephrosis even though urea clearance is initially normal transient depression of the urea clearance may be observed during diuresis. In advanced renal insufficiency and in acute diffuse glomerulonephritis the use of mercury in any form is dangerous. Even with good kidney function slight increase in cast excretion has been described. It is undesirable to produce excessive diuresis in weak and grossly edematous patients since too rapid depletion of water and chloride may lead to increased weakness, restlessness, mental confusion or even circulatory collapse.³⁰

3 Additional Measures Used in Treating Nephrotic Edema
Thyroid substance and thyroxin induce diuresis in some cases of nephrosis although the mechanism of their action is not clear. Epstein³¹ impressed by certain similarities between myxedema and nephrosis found that patients with the nephrotic syndrome could be given relatively large doses of thyroid substance without toxic symptoms or elevation of basal metabolic rate. At first small doses should be used with repeated determination of the basal metabolic rate. If toxic symptoms do not develop dosage is increased gradually until as much as 1 Gm. (15 grains) per day may be given continuing for long periods if necessary. Toxic symptoms generally do not develop as long as hypercholesterolemia is present. Thyroid substance is always used merely as an adjunct measure in combination with high protein diet and other medical treatment.

Blood transfusion is logical therapy in nephrotic edema particularly if anemia is present. The transfusion of whole blood adds both erythrocytes and plasma proteins; it should theoretically correct one of the faults in the hypoproteinemic edema of nephrosis. However proteinuria often increases immediately after transfusion and it is probable that the added plasma protein is quickly lost in the urine. Nevertheless several transfusions of the usual size at intervals of three or four days frequently

improve appetite and assist the action of the usual diuretic drugs. Specially prepared concentrated lyophilized serum has also been used in treating nephrosis in childhood.³⁰ In hypoproteinemia, complicated by cardiac failure or by advanced renal insufficiency with hypertension and cardiac hypertrophy, transfusions are dangerous because of the temporary burden placed upon the heart. In pure nutritional edema transfusion produces dramatic relief while high protein diets act more slowly.

Acacia, an inert colloid, was advocated for the treatment of nephrotic edema by Hartmann and Senn,³² who gave intravenously an amount calculated to be enough to raise the colloid osmotic pressure of the blood to 17 mm. Hg,—the so-called edema level. Large doses are, however, undesirable because of occasional severe circulatory reactions and because of probable harmful deposition in the liver.³³ It has been our custom to reserve the administration of acacia for otherwise intractable cases of nephrotic anasarca without hypertension or renal insufficiency. After all other therapeutic measures have by specific trial proved unsuccessful, these patients are given not more than 200 Gm (6½ ounces) in divided doses.³⁴ It is desirable to test the patient for sensitivity to acacia by intradermal injection since hypersensitivity, though rare, does occur. The first injection should be small, preferably 5 or 10 Gm (1¼ to 2½ drams), and later dosage should not exceed 30 Gm. (7½ drams) daily in six per cent solution until a total of 200 Gm (6½ ounces) has been given. To avoid reactions it is best to administer a sedative, to inject the solution very slowly, and to avoid commercial solutions of acacia which are dark in color. This procedure produces satisfactory diuresis and temporary relief of edema in some otherwise refractory cases of nephrotic edema. It is probable that temporary increase in blood volume is the stimulus which starts diuresis.³⁵ The administration of acacia is contraindicated by liver disease, cardiac insufficiency, or hypertension.

Decapsulation of the Kidneys has been advocated occasionally, but is not advisable except as a last resort.

4. **Additional Measures Used in Cardiac Edema:** Cardiac edema, being due to cardiac insufficiency, will be relieved by any procedure which improves circulatory function. Rest in bed, sedatives, and *digitalis* may be all that is required in mild cases to initiate a copious diuresis and free the patient of edema. *Venesection*, by reducing venous pressure

and restoring compensation is also often followed by diuresis particularly in patients with acute congestive failure. In all cases appropriate therapy of myocardial failure (see Chapter XXXIV) is a necessary prerequisite for the successful therapy of cardiac edema even when diuretics are used. For chronic cardiac failure with hypoproteinememia from malnutrition a high protein diet is advisable as cardiac recovery restores gastrointestinal function to normal.

5. Vicarious Elimination of Water. *Sweating* by heat or by diaphoretic drugs a favorite remedy of earlier days has fallen into disuse because of inefficiency, danger of chilling and likelihood of exhaustion. Weak patients find sweating induced by either heat or drugs extremely tiring. Edematous patients also frequently fail to sweat with diaphoretic measures which cause normal individuals to sweat profusely.

Purgation if drastic eliminates significant amounts of both water and salt by bowel but is too weakening to be generally useful. It is advantageous to keep the stools relatively soft but continued watery stools are undesirable.

Thoracentesis and *paracentesis abdominis* are frequently necessary in massive edema to relieve dyspnea. A tense ascites from any cause is often associated with profound anorexia and gastrointestinal distress which can be improved merely by paracentesis. Moreover relief of intra-abdominal pressure by paracentesis removes external pressure from the abdominal and renal veins and is said frequently to increase the effectiveness of diuretic drugs.

Southey's tubes must be used occasionally although the need for subcutaneous drainage has diminished since the introduction of the more powerful diuretics and the general use of water and salt restriction. Because of the danger of infection such drainage should be reserved for cases with enormous edema which has resisted all other measures. Rigid asepsis is essential. When the cannulae are properly inserted into the legs very large amounts of fluid can be drained off since edema elsewhere and serous effusions are reduced as the fluid migrates to the drained extremities. Even though the tubes are removed after 24 to 48 hours strict asepsis must be continued until the skin heals completely. This may require several days because edema fluid usually continues to ooze from the cutaneous wounds after the cannulae have been removed.

IV CLINICAL EXAMPLES

NEPHRITIC EDEMA

C W white male aged 34 developed malaise severe headache puffiness of the face edema of the ankles and oliguria following the last of several mild sore throats in previous months. The patient was seen three days after the onset of symptoms. At this time it was noted that body weight had increased from the usual 70 to 80 kg (150 to 170 pounds). The urine was scanty in amount and dark in color but gross hematuria had not been observed.

Physical Examination The blood pressure was 128 systolic and 80 diastolic with normal temperature pulse and respiration. The pharynx was reddened and the tonsils were chronically infected. The lungs were negative. The heart peripheral vessels and retinal vessels were normal. The ankles and face were obviously edematous.

Laboratory Studies The blood count was normal. Urinary output during the first 24 hours was 400 cc with a specific gravity of 1.027. The urine contained moderate albumin and an Addis count revealed that in 12 hours 8 000 000 casts were excreted (normally 5000 or less) with 11.0 per cent blood casts 10 000 000 red cells (normally 0.5 million or less) were excreted in the same period. In the first few days the blood urea nitrogen rose from 24 to 41 mg per cent. The concentration of the plasma proteins was 6.2 Gm per cent. The urea clearance was 22 per cent of normal. The blood sedimentation rate was rapid.

The patient was given no fluids whatever for 24 hours along with a soft diet low in salt and poor in protein. Thereafter fluids were restricted to 750 cc per day until diuresis began on the fourth day of hospitalization. Fluid intake was then increased to 2000 cc per day as diuresis continued and the diet was rapidly increased so that at the end of the first week the patient was receiving at least 70 Gm of protein per day. The spontaneous diuresis rapidly reduced body weight from a maximum of 175 pounds to 152 pounds as edema disappeared. The blood urea nitrogen fell to normal and urea clearance rose to 65 per cent of average normal function within a few days. The urine still contained many casts and erythrocytes. The infected tonsils and one infected tooth were removed three weeks after admission. Subjectively the patient felt well as soon as the spontaneous diuresis began. Rest in bed was continued for a period of eight weeks after which the patient was allowed to return home for a further rest period of several months before work was resumed. Except for a minor recrudescence about one year later healing progressed uninterruptedly and at the present time (five years later) there are no detectable signs of active renal disease the urine being negative by Addis count.

Comment Bed rest restriction of fluid and salt and temporary restriction of protein were followed by spontaneous diuresis with prompt relief of edema and azotemia. Local infection was treated only after recovery was well established. It is not advisable to use diuretics in treating this form of edema. It is essential however to continue bed rest and to restrict activity for months after the acute attack. Protein intake should be returned to normal as soon as possible in order that general nutrition be kept at a high level. It is also essential that focal infection be checked at frequent intervals.

NEPHROTIC EDEMA

S. H. white female aged 27 complained of oliguria and increasing edema having been perfectly well until 11 days before. The urine was dark but not hemorrhagic and there were no other symptoms. Recurrent tonsillitis in previous winters had led to tonsillectomy several months before the appearance of edema but there had been no recent infection.

Physical Examination The blood pressure was 112 systolic and 72 diastolic with normal temperature, pulse, and respiration. The pharynx contained residual tonsillar tissue which was not inflamed. Cardiac size and rhythm were normal. A high pitched murmur was heard over the mitral area throughout systole with a loud first sound but no thrill or presystolic murmur. The retinal and peripheral arteries were normal. Body weight had increased 20 pounds concurrently with the appearance of marked facial and peripheral edema, moderate ascites and slight bilateral hydrothorax.

Laboratory Studies The blood count was normal. Urinary output was as low as 280 cc. per 24 hours with specific gravities as high as 1.020 (1.028 when corrected for contained protein). From 50,000 to 1,000,000 casts were excreted in 12 hours (normally 5000 or less) including at various times all types excepting blood and failure casts. Initial specimens of urine were reported by routine examination to contain no red cells but according to Addis counts erythrocyte excretion varied at first from 0.2 to 0.7 million per 12 hours (normally 0.5 million or less). Albuminuria frequently exceeded 2.5 Gm. per 24 hours. The urine contained doubly refractive lipoids. Tests for syphilis were negative. Blood urea nitrogen, plasma chlorides and blood sugar were normal. The blood cholesterol was 823 mg. per cent, total plasma proteins 3.81 Gm. per cent and plasma albumin 1.31 Gm. per cent with reversal of the albumin-globulin ratio. The blood sedimentation rate was extremely rapid. Kidney function was normal as measured by concentrating power, urea clearance and phenolsulfonphthalein elimination. The basal metabolic rate was minus six per cent.

The clinical course and therapy during hospitalization are summarized in Fig. 2. Limitation of fluids, restriction of sodium chloride, a protein intake forced to tolerance, accompanied by full therapeutic dosage of thyroid substance, ammonium chloride, and urea failed to induce significant diuresis. An abrasion over the lumbar region became slightly inflamed and the danger of spreading infection in the conspicuously

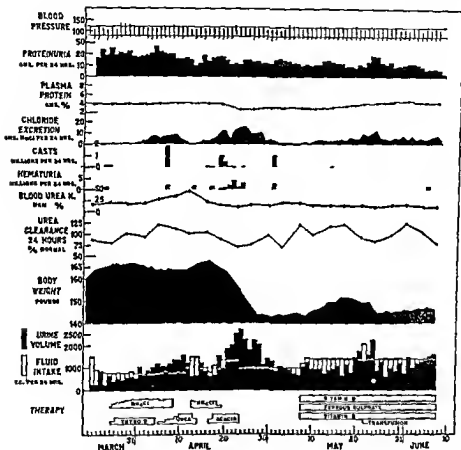


FIGURE 2 Chart illustrating clinical course and therapy of patient with nephrotic edema (Landis & Elsom: *Internat Clin*, J. B. Lippincott Co., Philadelphia)

edematous tissues became the primary consideration. Acacia was therefore administered intravenously in repeated doses of 10 then 20 Gm. per day until a total of 130 Gm. had been given. A conspicuous diuresis followed and edema disappeared as body weight decreased from 168 to 143 pounds.

Other foci of infection having been excluded, residual tonsillar tissue was removed by electrocoagulation. Vitamins and ferrous sulfate were added to the high protein diet. Edema fluid began to reaccumulate but a single transfusion induced renewed diuresis.

As shown in Fig 2 blood pressure and urea clearance were normal throughout as was the blood urea nitrogen except during the period when urea was given in doses as high as 80 Gm per day Chloride excretion increased without significant change in body weight while ammonium chloride was given and again during the diuresis and reduction in body weight which followed the administration of acacia The later rise in chloride excretion was produced by a gradual relaxation of salt restriction Ammonium chloride in doses of 10 Gm (21½ drams) per day reduced slightly the carbon dioxide combining power of the blood and was associated also with temporarily increased cast and erythrocyte excretion which persisted but did not increase further during the later diuresis from acacia Albuminuria decreased steadily and was not perceptibly changed by the massive diuresis The plasma proteins were 3.8 per cent on admission fell to 2.7 per cent after acacia was given and then rose slowly to reach 4.1 per cent at the time of discharge and 6.5 per cent six months later Repeated cast counts and blood studies since discharge from the hospital have shown continued improvement The most recent urine specimens have been normal with respect to specific gravity protein content and sediment

Comment The clinical diagnosis made in this case was (a) nephrotic syndrome probably due to true lipoid nephrosis and (b) rheumatic heart disease (inactive) Erythrocyte excretion in the urine was low initially and rose to slightly less than 2,000,000 per 12 hours only during the administration of large doses of ammonium chloride Under these conditions the finding of excessive red cell excretion did not seem to require that a diagnosis of glomerulonephritis be made

This case illustrates the usual difficulty encountered in inducing diuresis when the plasma proteins are extremely low The edema resisted the ordinary diuretics and was finally relieved by the intravenous administration of acacia A slight recurrence was apparently interrupted by a transfusion If spontaneous remission had not reduced the albuminuria and increased the concentration of the plasma proteins edema would doubtless have returned as soon as the temporary effects of the acacia and the transfusion were over

CARDIAC EDEMA

W. S. white male aged 16 complained of fatigue nocturnal dyspnea dry cough and swelling of the ankles These symptoms had begun approximately four weeks before with epigastric pain and severe dyspnea which interfered with sleep for approximately one week The family

physician prescribed bed rest in spite of which the legs and thighs became conspicuously swollen. Resumed activity shortly before admission led to return of epigastric pain, severe dyspnea and increased edema. Prior to admission digitalis had been administered in excess of usual therapeutic dosage.

Physical Examination The blood pressure was 150 systolic and 90 diastolic with normal temperature, a pulse rate of 56 and orthopnea with a respiratory rate of 25 to 30. The ankles, sacrum and abdominal wall were massively edematous. The retinal arteries showed early angiosclerosis without hemorrhages or exudates. The lungs were normal except for moist rales at the bases. The heart was enlarged, the left border being 13 cm. from the midline and the total area by orthodiagram being 88 per cent above the predicted normal. A systolic thrill was felt over the precordium. The rhythm was totally irregular owing (a) to auricular fibrillation and (b) to coupled beats. The murmurs of mitral stenosis and insufficiency were present. The peripheral vessels were somewhat thickened but not tortuous. The liver was tender and extended 4 cm. below the costal margin. The neck veins were distended.

Laboratory Studies The blood count was normal. The urine had a specific gravity of 1.025 or more on numerous occasions, contained moderate albumin and a few granular casts but no erythrocytes. Tests for syphilis were negative. The blood urea nitrogen on admission was 33 mg. per cent but rapidly fell to 9 mg. per cent. The blood sugar and plasma chlorides were normal. The plasma protein percentage was somewhat reduced, being 5.7 Gm. per cent. The electrocardiogram showed evidence of auricular fibrillation and possible coronary occlusion.

The patient had been overdigitalized prior to admission as indicated by the bradycardia and coupled beats. Bed rest, salt restriction and a low fluid intake failed to produce a significant diuresis. After nine days digitalis was resumed cautiously, also without effect on diuresis. In this interval the blood urea nitrogen fell to normal. Urea clearances and urines of high specific gravity indicated that the kidneys were normal, the azotemia being explained by the reduced function of passive congestion. A mercurial diuretic, mersalyl, was injected intravenously in doses of 1 and 2 cc. 48 hours after ammonium chloride had been started in doses of 5 Gm. (1 1/4 drams) per day. This procedure repeated at intervals of five days produced a diuresis between 3000 cc. and 4000 cc. on each occasion. Body weight decreased from 150 to 130 pounds in the course of three weeks, accompanied by symptomatic improvement and considerable recovery of cardiac compensation. The patient was discharged free of edema and moderately well compensated to a convalescent home.

Comment In this instance, in the presence of auricular fibrillation and profound decompensation, bed rest, salt and fluid restriction, and the administration of digitalis produced no diuresis. The use of a mercurial diuretic, associated with ammonium chloride, was justified by the observation that concentrating power was retained, the urine having a specific gravity as high as 1.030 on several occasions. The slight elevation of blood urea nitrogen did not contraindicate the use of mersalyl under these circumstances, because the mild azotemia was due to passive congestion rather than to intrinsic renal insufficiency. The relief of edema produced by the mercurial diuretic was unquestionably an important factor in improving cardiac function in this patient. The plasma protein percentage was slightly low, making the edema more difficult to treat than would have been the case if simple passive congestion had been associated with a completely normal plasma protein percentage. In this instance the edema was of mixed pathogenesis, being due in part to congestive failure and in part to hypoproteinemia which not uncommonly results from voluntary dietary restriction.

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- Angina pectoris (*continued*)
 in aortic insufficiency 374
 in hypothyroidism 265
 mechanism 405
 prognosis 412
 symptoms 408
 treatment 413
 surgical treatment 415
- Angina pectoris paravertebral sympathetic
 block for relief of pain in 1185
- anatomy and physiology 1185
 blocking of sensory pathways 1186
 results and sequelae 1192
 technic 1188
- Angina pectoris total thyroidectomy in 1231
- Angina pectoris traumatic 275
- Angiocardiography in congenital cardiac ab-
 normalities 36
- Angioma cavernous 1753
- Angioma simple 1750
- Anomalous bands and chordae 22
- Anomalous septa 14
- Anoxemia test of cardiac insufficiency 438
- Aorta ascending aneurysm of as complica-
 tion of cardiovascular syphilis 151
- Aorta coarctation and hypoplasia of 14
- Aorta dextroposition of 15
- Aorta hypoplasia of 26
- Aorta measurement by roentgenology 711
- Aorta medial cystic necrosis 4
- Aorta x ray visualization 697
- Aortic and mitral atresia 29
- Aortic arch
 double 26
 right 26
- Aortic arch and branches anomalies of 15
- Aortic arch aneurysm of as complication of
 cardiovascular syphilis 154
- Aortic coarctation adult type x ray diag-
 nosis 706
- Aortic dwarfism from stenosis of aortic valve
 24
- Aortic insufficiency capillaries in 1363
- Aortic media syphilitic necrosis 145
- Aortic septum localized defect of 27
- Aortic valve bicuspid 23
- Aortic valve disease 7 373
 aortic insufficiency 161 374
 in cardiovascular syphilis 150
 aortic stenosis 21 377
- Aortic valves rupture of 274
- Aortitis luetic x ray diagnosis 704
- Arborization block 565
- Arrhythmia absolute or perpetual 780
- Arrhythmia extrasystolic 271
- Arrhythmia sinus 9 749
- Arrhythmias electrocardiography 632
- Arrhythmias of unknown origin 4
- Atsphenamine in cardiovascular syphilis 169
- Arterial occlusion sudden 1632
- Arterial pressure high 1413
- Arterial pressure low 1498
- Arterial trunk common 7
- Arterial trunks transposition or reversed tor-
 sion of 15 28
- Arteries great transposition of 7
- Arteries peripheral aneurysm of 1688
- Arterio-capillary fibrosis 213
- Arteriography 1680 1707
- Arteriosclerosis 1511
 capillary sclerosis 1552
 clinical importance of arteriosclerosis of
 greater circulation 1556
 diabetes and arteriosclerosis 1557
 diagnosis 1561
 etiology 1547
 experimental arteriosclerosis 1553
 incidence 1544
 localization of 1545
 Monckeberg arteriosclerosis 1553 1557 1710
 pathogenesis 1513
 pathology 1511
 phlebosclerosis 1550
 primary arteriosclerosis 1552
 prophylaxis 1562
 pseudo or transient arteriosclerosis 1558
 relation of
 heredity 1559
 infections food metabolic products and
 poisons 1556
 race 1558
 treatment 1552
 diet 1561
 drugs 1564
 educational 1562
 exercise and rest 1563
- Arteriosclerosis capillaries in 1563
- Arteriosclerosis latent 213
- Arteriosclerosis obliterans 1691
 etiology 1691
 age 1691
 heredity 1699
 infectious acute and chronic 1699

- Arteriosclerosis obliterans,
 etiology (*continued*)
 lead, 1700
 manganese, 1700
 nutrition, 1696
 race and climate, 1694
 worry, exercise, hard work, 1700
 pathology and pathogenesis, 1709
 Mönckeberg's sclerosis, 1710
 true and false aneurysms in peripheral
 arteries, 1712
 signs and symptoms in extremities 1700
 absence of edema, 1702
 atrophy of
 muscles 1701
 skin and nails, 1701
 coldness of hand or foot 1702
 delayed venous filling time, 1701
 fatigue and weakness 1702
 gangrene, 1704
 numbness or formication, 1702
 pain of intermittent claudication 1703
 pains at night in calf and thigh muscles
 1704
 pallor on elevation and rubor followed
 by cyanosis on dependency, 1701
 rest pains in feet 1704
 tortuous arteries, 1702
 ulcers, 1701
 special examinations, 1705
 arteriography, 1707
 histamine flare tests, 1708
 measured work tests, 1709
 oscillometric readings, 1705
 reflex vasodilatation tests, 1706
 surface temperature studies 1706
 x rays 1707
 treatment 1715
 alcohol, 1715
 antiseptics, 1724
 baths, 1716
 contrast baths 1716
 hot, 1717
 sitz baths 1716
 soaks, 1717
 whirlpool baths 1717
 exercise, 1714
 intermittent venous hyperemia, 1722
 position 1713
 pressure suction boot treatment 1719
 rest, 1713
 Arteriosclerosis obliterans,
 treatment (*continued*)
 saline and other solutions intravenously,
 1722
 Saunders oscillating bed, 1721
 surgical aspects, 1721
 amputation, 1725
 tissue extracts, 1718
 tobacco, 1714
 vasodilating drugs, 1723
 Arteriosclerosis, pulmonary, in etiology of
 chronic pulmonary heart disease, 225
 Arteriovenous aneurysm congenital 1754
 Arteriovenous fistula, acquired 1676
 diagnosis, 1677
 etiology and physiology 1676
 treatment, 1679
 Arteriovenous shunt, lesions of 26
 Arteritis temporal, 1681
 Aschoff bodies, 46
 Asthenia neurocirculatory 1 12 201
 physical therapy in 1318
 Asthma, bronchial in etiology of chronic
 pulmonary heart disease 221
 Asthma, cardiac 1113
 total thyroidectomy in 1236
 Asynchronous action of two ventricles 793
 Atheroma and sclerosis of coronary vessels as
 cause of coronary disease 4
 Atheroma x ray diagnosis, 701
 Athlete's heart, 5
 Atresia of pulmonary, tricuspid aortic, and
 mitral valves, 15
 Atriaseptal defect, x ray diagnosis, 707
 Atrioventricular conduction time prolonga-
 tion of, as sign of arthritis in rheu-
 matism 52 59
 Atrioventricular node, 725
 Atrophy of heart, 6
 Atropine
 in acute pulmonary heart disease 221
 in heart block, 791
 Auricle, double left, 23
 Auricle, left x ray visualization 696
 Auricle, right, x ray visualization, 695
 Auricular and ventricular septa absence of
 29
 Auricular complex 556
 abnormalities of, 562
 Auricular contraction, heart sounds associated
 with 547

- Auricular extrasystoles 636
 Auricular fibrillation 10 69 269 613 780
 diagnosis 781
 etiology 783
 in coronary artery disease 393
 in hyperthyroidism 181
 in mitral stenosis 363
 pathogenesis 783
 pathology 783
 prognosis 781
 symptoms and complications 783
 treatment 786
 Auricular fibrillation and flutter caused by digitalis 1139
 Auricular flutter 10 271 611 775
 Auricular (P) wave lowering flattening or inversion of 9
 Auricular septal defect 7
 Auricular sound double 547
 Auricular standstill 616
 Auricular weakness or failure 12
 Auriculoventricular block 11 788
 Auriculoventricular cusps anomalies of 11
 Auriculoventricular heart block 616
 Auriculoventricular nodal escape 9
 Auriculoventricular nodal rhythm 10 619
 Auriculoventricular rhythm 751
 diagnosis 756
 prognosis 756
 therapy 756
 Auscultation of heart 478
 Auscultatory phenomena of 500 supposedly normal hearts table 480
 Austin Flint murmur 368
 Autogenous vaccine in bacterial endocarditis 155
 V V block 618
 A V heart block caused by digitalis 1139
 Avitaminosis electrocardiogram in 693
 A V node escape of pacemaker 10
 A V rhythm 754
 A V rhythm and V V dissociation caused by digitalis 1137
 Axis deviation 621
 abnormal electrical 11
 left axis deviation 621
 right axis deviation 625
 Ayerza's disease 226 1553
 B
 "Back pressure" as cause of congestive heart failure 1061
 Bacterial endocarditis 123
 Bacterial infection as cause of heart disease 2
 Bacteriology of rheumatic fever 87
 Barometric pressure effect on blood pressure 1337
 Basophilism pituitary 238
 Baths in treatment of arteriosclerosis obliterans 1716
 Bazett's formula calculation of electrical systole by C11
 Beaked T waves 628
 Beck operation results of 1180
 Beriberi and the heart 12 9
 chemical changes 1264
 differential diagnosis 1266
 electrocardiographic changes 1263
 hemodynamics of circulation 1263
 morphological changes 1261
 organic heart disease and beriberi 1267
 pathogenesis 1264
 role of alcohol 1265
 symptoms and signs 1260
 treatment 1263
 physical therapy 1317
 Beriberi as cause of cardiac pathology 5
 Beta methyl choline in auricular flutter 613
 Bicuspid aortic valve 23
 Bicuspid pulmonary valve 21
 Biloculate heart 7
 Bismuth arspenamine sulfonate in cardiovascular syphilis 169
 Bismuth in cardiovascular syphilis 171
 Bismuth subnitrate in hypertension 1462
 Blood changes in rheumatic fever 111
 Blood pressure effect of hydrotherapy on 1503
 Blood pressure high 1413
 Blood pressure low 1498
 Blood pressure normal and its physiologic variations 1390
 cold pressor test 1333
 normal blood pressure 1339
 desirability of using the mode and not the mean 1310
 discordance in results reported by different observers 1339
 influence of age 1311
 range of normal 1315
 sex 1315
 physiologic variations in normal 1329
 alcohol 1331

- Blood pressure, normal
 physiologic variations (*continued*)
 barometric pressure 1337
 body build 1335
 climate and temperature 1336
 constipation 1331
 differences in the two arms 1333
 diurnal variations 1330
 emotions 1331
 height and surface area 1336
 meals 1333
 menstruation and pregnancy 1334
 muscular effort 1333
 position of arm 1334
 posture 1329
 sleep 1330
 tobacco 1330
 weight 1333
 standardization of determinations 1322
 blood pressure equipment 1322
 determination of diastolic and pulse pressures 1323
 determination of systolic pressure 1323
 patient 1322
 position and method of application
 of cuff 1323
 of stethoscope 1323
 significance of palpatory and auscultatory levels 1323
- Blood sugar and hypotension 1517
- Blue disease 14
- Body build effect on blood pressure 1330
- Body fluids factors in normal distribution of 1797
- Body weight and build and low arterial pressure 1511
- Bradycardia sinoauricular 9
- Bradycardia sinus (simple) 630 739
- Branham's bradycardia phenomenon 1677
- Bromides in hypertension 1461
- Bronchial asthma in etiology of chronic pulmonary heart disease 221
- Buerger's disease 1579
- Bullet wounds of heart 1153
- Bundle branch block 11 565 580 790
 left as cause of left axis deviation 621
 right as cause of right axis deviation 620
- C**
- Cacodylate in bacterial endocarditis 155
- Calcification of heart 6
- Calcification of pericardium 7
 protodiastolic heart sound associated with 538
- Calcifications of heart and great vessels x ray visualization 698
- Capillary circulation 1300
 anatomy and physiology 1300
 hormone regulation 1303
 local regulation by substances formed in tissues 1302
 nervous regulation 1302
- Capillaries in disease 1361
- Clinical importance 1350
- Methods of clinical study 1351
 capillary fragility 1360
 Rumpel-Leede test 1360
 capillary permeability 1361
 capillary pressure 1300
 technic of determination 13 8
 visualization 1351
- Capillary fragility 1360
- Capillary permeability 1361
- Capillary pressure 1305
- Capillary pulse in aortic insufficiency 376
- Capillary sclerosis 15 2
- Carbon dioxide mineral bath 1300
- Cardiac abnormalities congenital 14
- Cardiac aneurysm 6
 x ray diagnosis 703
- Cardiac asthma 351 1113
 in coronary artery disease treatment 101
 total thyroidectomy in 1206
- Cardiac diet 1098
- Cardiac dyspnea paroxysmal 1112
- Cardiac edema 1797
- Cardiac efficiency faulty 12
- Cardiac enlargement extrinsic causes 703
- Cardiac failure 329
 acute 1062
- Cardiac hypertrophy and dilatation 329
 circulatory failure 300
 diagnosis 334
 inspection and palpation 331
 percussion 338
 electrocardiography 339
 functional evaluation and prognosis 318
 pathology mechanism and development 339
 radiology 313
 treatment 305

- Cardiac in industry, 1018
 training in sheltered workshops, 1037
 vocational possibilities for heart patients 1054
- Cardiac insufficiency venous pressure in 1376
- Cardiac neuroses 5 196
- Cardiac overstrain primary 281
- Cardiac pain clinical associations of 431
- Cardiac patient as a surgical or obstetrical risk 492
 obstetrical considerations 501
 care of heart in pregnancy 502
 effect of pregnancy on normal heart 501
 surgical considerations 492
 differential diagnosis 492
 estimation of surgical risk 496
 prognosis *versus* surgical risk 493
 significance of symptoms 495
- Cardiac rate during normal sinus rhythm
 influence of digitalis on 1137
- Cardiac rupture 7
- Cardiac standstill 633
- Cardiac symptoms of arterial hypertension 1436
- Cardiac tamponade 303
- Cardiac trauma 268
- Cardiac valves operations on 1189
- Cardiorespiratory murmurs 181
- Cardiovascular ability 12
- Cardiovascular efficiency faulty 12
- Cardiovascular syphilis 133
- Cardiovascular system and hypotension 1313
- Carditis rheumatic 43
 signs and symptoms 52
 treatment 71
- Carotid sinus pressure effects of 612
- Carotid sinus syncope electrocardiogram in 684
- Case reports
 acute and recurrent bundle branch block and acute rheumatic carditis 796
 aneurysm filling upper mediastinum 156
 aneurysm in sinus of Valsalva 153
 aneurysm of ascending aorta and aortic arch 151
 anginal attacks cured by subtotal thyroidectomy 407
 angina pectoris traumatic 276
 angina syndrome pernicious anemia as precipitating agent 212
 aortic involvement early in syphilis 139
- Case reports (continued)
 aortic mitral and tricuspid valvular disease 369
 aortic stenosis 378
 arteriovenous fistula 1677
 asymmetry in blood pressure due to syphilitic aneurysm 1417
 auricular fibrillation 269 270
 high grade that was overdigitalized 785
 auricular flutter and AV heart block caused by digitalis 1139
 auricular flutter changed to fibrillation by digitalization 777
 auricular flutter that responded directly to quinidine therapy, 779
 auriculoventricular rhythm following painless coronary thrombosis and myocardial infarction 755
 avoidance of surgery in a cardiac patient 496
 bradycardia of catarrhal jaundice 742
 Cappelen's case of surgery of heart 1145
 cardiac contusion 1163
 cardiac dilatation acute and congestive failure associated with polyneuritis 1287
 cardiac edema 1822
 cardiac standstill as cause of death from quinidine, 1225
 cardiovascular syphilis with aneurysm of ascending aorta 13
 carditis as the only manifestation of rheumatic fever 69
 carotid sinus collapse or so called vagus fainting 745
 carotid sinus episodes resulting from reflex inhibition of heart 746
 cervical rib causing asymmetry in blood pressure 1116
 cholelithiasis with symptoms resembling coronary disease 454
 chronic constrictive pericarditis death after operation 326
 chronic constrictive pericarditis successful result of operation in a severely crippled child 319
 chronic constrictive pericarditis successful result of operation in a young man with moderate involvement 320
 chronic constrictive pericarditis successful result from two risky operations in a seriously crippled middle aged man 322

Case reports (continued)

- congestive failure of circulation and polyneuritis improvement after B₁ therapy 1278
- congestive failure of circulation cardiac asthma polyneuritis, and mild psychosis improvement on high vitamin diet and continuous high alcohol intake 1285
- congestive failure of circulation polyneuritis and Korsakoff's psychosis improvement on vitamin B₁ 1273
- congestive failure of circulation severe mild pellagra and polyneuritis and fatal circulatory collapse 1270
- congestive failure of circulation the only manifestation of vitamin deficiency 1281
- coronary disease and cholelithiasis 455
- coronary heart disease 15
- coronary insufficiency showing value of anoxemia test 440
- coronary insufficiency sudden death with previous negative physical examination and electrocardiographic findings 435
- digitalis bigeminy following diuresis 767
- digitalis medication effects of on patient with severe heart disease and cardiac decompensation 1012
- digitalis medication effects of with five different preparations 1010
- effects of digitalis on rate rhythm and mechanism of heart 1137
- emphysema of mediastinum spontaneous 482
- endocarditis simulating typhoid fever in its onset 131
- endocarditis undiagnosed hemiplegia 152
- endocarditis undiagnosed uremia 152
- erythremalgia high concentration of venous blood oxygen 1611
- erythremalgia relation between distress and temperature of skin 1610
- extrasystole causing irregular heart action relieved by thyroid extract and potassium iodide 759
- extrasystoles and ventricular paroxysmal tachycardia caused by digitalis 1140
- febrile tachycardia of lobar pneumonia 731
- gonococcal arthritis severe 130

Case reports (continued)

- heart block with Adams Stokes attacks relieved by atropine and ephedrine, 794
- heart disease congenital with tetralogy of Fallot 13
- hypertension and anemia 1469
- hypertension and nephritis low salt diet 1519
- hypertension bismuth subnitrate therapy 1465
- hypertension dangers of thiocyanate therapy 1463
- hypertension diagnostic problems 1411
- hypertension induced by psychogenic factors 1456
- hypertension in pregnancy 1416
- hypertension irritation from a focus of infection as contributory cause 1456
- hypertension provoked by chronic plumbism oral sepsis and anemia 1456
- hypertension renal function tests in 1445
- hypertension therapy based on etiology cholecystitis and medullary tumor of adrenal 1427
- hypertension therapy based on etiology chronic plumbism anemia oral sepsis and secondary chronic renal impairment 1425
- hypertension therapy based on etiology chronic post scarlet fever nephritis preexistent hypertensive disease exacerbated by pregnancy anemia 1426
- hypertension therapy based on etiology hereditary vulnerability to vascular disease obesity anxiety fatigue in adequate fluid intake 1426
- hypertensive heart disease 13
- hyperthyroidism effect of quinidine on auricular fibrillation 192
- hyperthyroidism with dilatation of ventricles 187
- hyperthyroidism with marked cardiac dilatation and hyaline and fatty degeneration of muscle fibers 191
- hypotension for 28 years 1535
- hypotension for 25 years 1535
- hypotension for 20 years 1535

Case reports (continued)

- hypotension, physiotherapy in 1536
- irritable normal heart 15
- lymphedema primary, 1618
- lymphedema, secondary, inflammatory, 1621
- myocardial injury, 277, 278
- nephritic edema, 1819
- nephrotic edema, 1820
- obesity hypertensive arteriolar disease with myocardial weakness and pulsus alternans or alternation, 800
- painful attacks resembling anginal paroxysms without signs of organic cardiac or vascular disease, 435
- paroxysmal auricular fibrillation responding to quinidine 781
- paroxysmal auricular tachycardia with syncope attacks controlled by physiotherapy and potassium iodide 768
- paroxysmal ventricular tachycardia electrocardiogram, 772
- periarthritis nodosa 1575
- physiological reaction produced by apprehension 1107
- pneumococcal endocarditis mistaken for empyema, 151
- primary cardiac overstrain 282
- purulent pericarditis, 1167
- quinidine in an elderly patient 1197
- quinidine in auricular fibrillation, 1193
- rapid heart action of asthmatic bronchitis and adrenalin administration 733
- restoration of normal sinus rhythm in chronic auricular fibrillation by use of quinidine, 1203
- rheumatic fever acute fulminating 51
- rheumatic fever, erythema as the only manifestation, 106
- rheumatic heart disease, 15
 - chronic active, 55
 - persistently inactive, 58
 - recurring 57
- rupture of left ventricle 276
- shock from dehydration 1402
- shock from hemorrhage from an inflamed bowel 1403
- sinus arrhythmia 750
- sinus bradycardia and attacks of fainting due to sinoauricular standstill resulting from hyperirritable carotid sinus reflex 744

Case reports (continued)

- sinus bradycardia of increased intracranial pressure, 741
- syphilitic myocarditis, 157
- tachycardia of neurovascular asthenia, 732
- tachycardia, psychogenic, 731
- temporal arteritis, 1681
- thromboangitis obliterans and bone atrophy, 1597
- thromboangitis obliterans and thrombosis of carotid artery, 1600
- thromboangitis obliterans of coronary arteries, 1596
- thromboangitis obliterans of digital and palmar arteries 1596
- thromboangitis obliterans of superior labial coronary arteries, 1599
- total thyroidectomy in
 - angina pectoris 1244 1250
 - chronic heart disease, 1216
 - paroxysmal dyspnea, 1247
 - rheumatic heart disease mitral stenosis and regurgitation, and auricular fibrillation 1249
- toxic tachycardia of hyperthyroidism with myocardial damage, 735
- traumatic valvular disease, 273, 274
- two to one heart block relieved by atropine, 791
- venous pressure in syphilitic aortitis 1373
- Cavernous angioma 1733
- Cerebral aneurysm 1686
- C factor, 18
- Chemical thrombophlebitis 1652
- Cheyne Stokes respiration in left ventricular failure, 351
- Chuan, network of 22
- Chloride metabolism and arterial pressure, 1519
- Cholesterol arteriosclerosis 1551
- Chordae, anomalous, 22
- Chorea and rheumatic fever, 107
- Chorea, Sydenham's, as cause of heart disease 2
- Chromaffin cell tumors benign, of suprarenals, 267b
- Circulatory failure, 350
- Circulatory function, studies of in chronic pulmonary heart disease, 250
- Circulatory measurements abnormal in chronic pulmonary heart disease, 250

- Circulatory rate determination 487
 Circus movement 10 639
 Cirsoid aneurysm 1753
 Claquement meso systolique pleuro pericardiale 525
 Classification of cardiac cases 1031
 Claudication pain of intermittent 1703
 Click midsystolic 521
 Click systolic 480
 Climate and hypotension 1526
 Climate effect on blood pressure 1336
 Clubbing of fingers in cyanotic group of congenital cardiac abnormalities 30
 Clubbing of finger tips as symptom of bacterial endocarditis 129
 Coarctation of aorta 14
 adult type 23
 x ray diagnosis 706
 Cod liver oil in excess as cause of injury to heart 5
 Coeur en sabot 707
 Cold pressor test 1338 1432
 Colds acute and hypotension 1527
 Common arterial trunk 7
 Compensation and trauma of heart 295
 Compensatory pause 475
 Complete heart block 792
 Compression of heart 1148
 acute compression triad 1150
 chronic compression triad 1152
 due to scars 1169
 physiology 1148
 Compression of heart chronic 305
 Contato's disease 307
 Concretio cordis 305
 Conduction disturbances of 11
 Congenital anomalies of cardiac chambers septa and great vessels 7
 Congenital cardiac abnormalities 14
 complications 31
 diagnosis 32
 etiology and pathogenesis 16
 pathology 19
 prognosis 37
 symptoms 29
 treatment 37
 Congenital cardiovascular defects 1 6
 physical therapy in 1315
 Congenital lymphedema 1619
 Congestion chronic passive in rheumatic heart disease 48
 Congestive failure 12
 in rheumatic fever, 115
 total thyroidectomy in 1231
 Congestive heart failure 236 442 1060
 capillaries in 1362
 complications and sequelae 1065
 differential diagnosis 1065
 pathogenesis and mechanism 1060
 prognosis 1066
 symptoms and signs 1063
 therapy 1067
 aftercare 1108
 aim of treatment 1067
 cathartics and laxatives 1097
 diet 1092
 digitalis 1071
 administration of 1078
 by routes other than mouth 1082
 indications for digitalis therapy 1076
 other drugs of digitalis series 1082
 therapeutic action 1072
 toxic effects 1071
 drainage of subcutaneous edema 1100
 drugs other than digitalis 1081
 diuretics 1097
 paracentesis 1100
 prevention 1110
 psychotherapy 1110
 rest 1068
 sedatives and hypnotics 1070
 surgery 1101
 thoracotomy 1102
 total thyroidectomy 1101
 treatment of associated diseases 1105
 treatment of complications 1102
 venesection 1099
 Constipation effect on blood pressure 1331
 Constrictive pericarditis chronic 305
 Contrast baths in treatment of arteriosclerosis obliterans 1716
 Contusion of heart 275 1157
 Cor batriatum trilobulare 29
 Corbiloculare 15 29
 Coronary artery disease 387
 anatomy 387
 anastomosis 389
 conduction system 388
 angina pectoris 405
 diagnosis 410
 findings 410
 mechanism 405

- Coronary artery disease,
 angina pectoris (*continued*)
 prognosis, 412
 symptoms, 408
 treatment, 413
 surgical treatment, 415
 coronary occlusion, 416
 diagnosis, 423
 differential diagnosis, 424
 symptoms, 418
 electrocardiographic findings 421
 physical findings, 420
 temperature and leukocyte count, 421
 coronary thrombosis, 424
 prognosis 424
 treatment, 426
 diagnosis, 397
 electrocardiographic findings, 396
 pathology, 399
 prognosis 398
 symptoms, 392
 treatment, 398
 Coronary artery disease, physical therapy in, 1317
 Coronary artery occlusion, 416
 complicating syphilitic aortitis, 159
 Coronary artery sclerosis vascularized grafts for, 1179
 Coronary disease (including angina pectoris), 445
 etiology, 448
 treatment, 458
 Coronary insufficiency, 12
 Coronary insufficiency, diagnosis, 431
 anoxemia test, 438
 clinical associations of cardiac pain, 431
 congestive heart failure, 442
 criteria indicating abnormal electrocardiographic response 439
 diagnosis, 432
 signs, 433
 symptoms, 432
 differential diagnosis, 436
 Coronary occlusion 591, 639
 x ray diagnosis 708
 Coronary sclerosis ligation of coronary veins for, 1180
 Coronary thrombosis physical therapy in 1317
 Coronary vessels disease of, 7
 Cor pulmonale
 acute 3 215
 chronic, 4 221
 electrocardiography in 677
 Corrigan (waterhammer) pulse in aortic insufficiency 375
 Cortical tumors and hyperplasia of suprarenals, 267a
 Cor triloculare, 15
 Coved T waves 627
 Crunch sternal, 480
 Cushing's syndrome, 258
 Cyanopathia, 14
 Cyanose tardive, 15
 Cyanosis congenital, 14
 pathogenesis 18
 Cyanosis retinae in congenital cardiac abnormalities, 30
 Cyanotic group of congenital cardiac abnormalities, 15, 28
 symptomatology, 30
 Cylindruria and rheumatic fever, 117
 Cystic necrosis, medial, 4
- ## D
- Deficiency diseases and the heart 1252
 beriberi, 1250
 chemical changes 1264
 differential diagnosis, 1266
 electrocardiographic changes, 1263
 hemodynamics of circulation, 1263
 morphological changes, 1261
 organic heart disease and beriberi 1267
 pathogenesis 1261
 role of alcohol 1265
 symptoms and signs 1260
 treatment 1268
 general undernutrition and inanition, 1254
 pernicious anemia deficiency of certain nutritional factors in 1257
 scurvy, 1291
 water and salt deficiency, 1256
 Deficiency diseases as cause of heart disease, 5
 Delirium cordis 780
 Depropenex in arteriosclerosis obliterans, 1718
 Descrescent arteriosclerosis of senescence, 1562
 Dextrocardia, 6
 congenital, 15, 20
 as cause of right axis deviation, 626
 Dextrocardiogram, 579
 Dextroversio cordis, 20
 D factor, 18
 Diabetes and arteriosclerosis 1557
 Diabetes mellitus, 267c
 and hypotension 1530
 Diabetic acidosis electrocardiogram in, 677
 Diet in rheumatic heart disease 72 75

- Diet relation to arteriosclerosis 1536
 Digitaline 1009
 Digitalis
 effects on
 electrocardiogram 1130
 electrocardiogram of precordial leads 1142
 changes in R-S T in association with large initial downward deflection 1143
 deviation of R S T in association with small or absent initial downward deflection 1143
 P wave of electrocardiogram 1136
 rate rhythm and mechanism of heart 1137
 auricular fibrillation and flutter 1139
 A V heart block 1139
 A V rhythm and A V dissociation 1137
 extrasystolic disturbances 1140
 influence on cardiac rate during normal sinus rhythm 1137
 ventricular paroxysmal tachycardia 1140
 T wave and S T segment of electrocardiogram 1130
 T waves and S T segments of normal hearts 1131
 T waves of badly diseased hearts 1131
 Digitalis
 in angina pectoris 415
 in auricular fibrillation 645
 in auricular flutter 642
 in cardiac enlargement 353
 in chronic pulmonary heart disease 231
 in congestive heart failure 1071
 in coronary artery disease 402
 in coronary thrombosis 426
 in paroxysmal tachycardia 774
 in rheumatic heart disease 73
 Digitalis dosage 1079
 Digitalis preparations clinical efficacy of 1001
 choice of preparation 1007
 indications 1001
 method of administration 1001
 method of evaluation 1011
 Digitalis toxic effects 1071
 Digoxin 1010
 Dilatation and hypertrophy of heart in hyperthyroidism 185
 Dilatation of heart 6 329
 Diphtheria
 T waves 697
 as cause of myocardial necrosis 2
 electrocardiogram in 682
 spontaneous 1808
 in chronic pulmonary heart disease 231
 Double auricular sound 547
 Double left auricle 23
 Ductus arteriosus 15
 patent 28
 Ductus arteriosus patent ligation of 38 1174
 operative procedure 1176
 results after ligation 117
 selection of patients 117
 Duroziez's sign in aortic insufficiency 376
 Dwarfism pituitary 257
 Dyspnea acute paroxysmal cardiac 1113
 Dyspnea in cyanotic group of congenital cardiac abnormalities 30
 Dyspnea paroxysmal as symptom of cardiovascular syphilis 147
 Dyspnea paroxysmal cardiac 1112
 Dyspnea paroxysmal total thyroidectomy in 1233
- ## E
- Ectopia cordis 6 20
 abdominalis 11
 Ectopic auricular rhythms 11
 Ectopic regular rhythms 753
 Ectopies 760
 Edebohls operation of renal decapsulation for essential hypertension 230
 Edema of extremities due to lymphedema 1616
 Edema pathogenesis and treatment of 1796
 factors in normal distribution of body fluids 1797
 factors in pathogenesis of edema 1800
 capillary pressure 1801
 disturbed innervation 1807
 fluid intake 1807
 heat 1807
 hypoproteinemia and reduced colloid osmotic pressure of blood plasma 1802
 lymphatic drainage 1805
 permeability of capillary wall 1805
 sodium chloride intake 1806
 tissue pressure 1803
 treatment 1810
 cardiac edema additional measures 1817
 diuretic drugs 1813

Edema

treatment (*continued*)

general measures 1810

diet 1812

restriction of salt intake 1811

restriction of water intake 1811

nephrotic edema additional measures 1816

vicarious elimination of water 1818

Edema subcutaneous drainage of in con

gestive heart failure 1100

Effleurage 1301

Effort syndrome 4 12 201

Einthoven's law and triangle 567

Einthoven's vector 573

Electrical axis 621

Electrocardiogram effects of digitalis on 1130

Electrocardiogram form of 535

angina pectoris 599

auricular complex abnormalities of 562

bundle branch block 590

coronary occlusion 591

dextrocardiogram and levocardogram 579

Einthoven's law and triangle 567

normal electrocardiogram 535

precordial and esophageal leads 574

preponderance 584

P R interval 562

Q R S deflections abnormally large or
small notch ng of Q R S 591

Q R S interval 563

T deflection 592

Electrocardiographic changes

in acute glomerulonephritis 210

in acute pericarditis 298

in angina pectoris 410

in beriberi 1263

in cardiac contusion 1162

in cardiac hypertrophy and dilatation 339

in chronic constrictive pericarditis 311

in coronary artery disease 396

in coronary insufficiency 438

in cor pulmonale 677

in hyperparathyroidism 261

in hypoparathyroidism 260

in hypothyroidism 266

in left ventricular failure 1113

in pulmonary embolism 677

in rheumatic fever 116

Electrocardiographic findings

in chronic pulmonary heart disease 299

in coronary occlusion 421

in rheumatic heart disease 59

Electrocardiography 602

abnormalities and variations of individual
waves in limb leads and certain
time intervals 613

abnormalities of P R interval 613 615

abnormalities of Q R S complexes 616

abnormalities in amplitude 617

increased amplitude 617

low amplitude 618

alternation in amplitude 620

prominent Q waves 616

slurring and notching 620

widening 620

abnormalities of Q T interval 626

abnormalities of T wave 626

diphaseic T waves 627

inverted T waves 627

coved T waves 627

notching of T waves 627

variations in amplitude 626

deviation of S T segment 628

electrical axis 621

significance of deep S waves in Lead II

with left axis deviation 623

U waves 629

arrhythmias 632

auricular disturbances dependent on a
circus movement 639

auricular fibrillation 643

drugs in 645

auricular flutter 641

circus movement 639

auricular extrasystoles 636

auricular paroxysmal tachycardia 638

auricular standstill 646

auriculoventricular nodal rhythm 649

A V nodal extrasystoles and nodal
paroxysmal tachycardia 629

ventricular escape f 2

classification 633

intraauricular block 646

normal mechanism 632

prolonged sinus pauses (cardiac stand
still) 635

pulsus alternans 638

sinuauricular heart block 635

sinus arrhythmia 633

ventricular extrasystoles 633

ventricular fibrillation 638

ventricular paroxysmal tachycardia 636

- Electrocardiography (*continued*)
 coronary occlusion 659
 physiological considerations, 660
 electrocardiogram in
 acidosis (nonrenal etc.) 678
 alkalosis 678
 anemia 683
 avitaminosis, 683
 cardiac syncope 684
 congenital cardiac abnormalities 31
 diabetic acidosis 677
 diphtheria 682
 hypercalcemia 679
 hypertension 682
 hyperthyroidism 679
 hypocalcemia 678
 hypoglycemia 678
 hypothyroidism and myxedema 679
 nephritis acute 691
 pneumonia 681
 rheumatic fever 680
 scarlet fever 681
 uremia 682
 instrument and method 603
 leads 605
 nomenclature 605
 technic 604
 myocardial infarction 662
 anterior myocardial infarction 662
 acute stage (stage of R-T deviation)
 663
 chronic stage (stage of permanent
 change in Q-R-S-T complex) 663
 electrocardiographic patterns stimulat-
 ing acute anterior infarction 667
 subacute stage (stage of rapidly chang-
 ing T waves) 661
 variations of usual pattern 666
 anteroposterior myocardial infarction 671
 conditions in which electrocardiogram
 fails to reveal myocardial infarction
 671
 infarction of lateral wall to left ventricle
 673
 posterior myocardial infarction 667
 normal electrocardiogram in the three limb
 leads 607
 comparison of time relations of electro-
 cardiogram with certain mechanical
 events 611
 excitation process 611
- Electrocardiography,
 normal electrocardiogram (*continued*)
 Q-T interval 610
 relation of ventricular complexes in
 three indirect leads 610
 pericarditis acute 675
 precordial leads 630
 abnormalities 631
 normal precordial leads 630
 pulmonary embolism and cor pulmonale
 677
 rôle of electrocardiogram in cardiac diag-
 nosis 602
 limitations 603
 Elephantiasis nostris streptigenes 1620
 Embolism 8
 Embolism and thrombosis of arteries of ex-
 tremities sudden 1632
 course of events in sudden arterial occlu-
 sion 1643
 diagnosis 1641
 etiology 1632
 pathologic changes following embolism
 1645
 prognosis 1645
 symptoms 1636
 interpretation 1638
 treatment 1647
 Emotions effect on blood pressure 1331
 Emphysema heart 222
 Emphysema mediastinal heart sounds due
 to 516
 Endocardial disease 7
 Endocarditis bacterial 123
 etiology 124
 incidence 123
 management 131
 pathology 127
 prevention 126
 recognition 129
 Endocarditis rheumatic, 47
 Endocrines and hypotension 1520
 Energy index of circulation 1501
 Enlargement of heart 329
 Epileptiform seizures in congenital cardiac
 abnormalities 30
 Epinephrine in erythremalgia 1615
 Epistaxis in rheumatic fever 109
 Ergosterol irradiated in excess cause of in-
 jury to heart 5
 Erythema in rheumatic fever 105

- Erythralgia (erythromelalgia) of extremities, 1605
 diagnosis, 1608
 methods of study, 1609
 nature of distress, 1608
 pathologic physiology, 1606
 hydrostatic pressure, 1607
 increased temperature of skin 1606
 susceptible state of skin, 1608
 vasoconstriction, 1608
 vasodilatation, 1607
 treatment, 1613
- Erythrocyte sedimentation rate, increased as a sign of carditis in rheumatism, 52
- Erythroltetranitrate in hypertension 1462
- Erythromelalgia of extremities 1605
- Esophageal leads, 578
- Essential hypertension, 243 1413
 cold pressor test in 1339, 1432
 etiology, 253
 pathogenesis, 247
 prognosis, 254
 treatment, 254
- Etiological classification of cardiovascular disease, 1
- Eupaverine in acute pulmonary heart disease, 221
- Evening dyspnea, 1114
- Ewart's sign 295, 303
- Excitation process in electrocardiography, 611
- Exercise in heart disease, 1297
- Exercise tolerance in rheumatic fever, 112
- Exertional dyspnea, 350
- Extracardiac anastomoses, 465
- Extrapolation triple method of measuring cardiac output 486
- Extra sounds associated with heartbeat, table, 550
- Extrasystoles 760
 auricular, 636
 A V nodal 632
 ventricular, 633
- Extrasystolic arrhythmia 271
- Extrasystolic disturbances caused by digitalis, 1140

F

- Fallot, tetralogy of 15, 24 28
- Familial tendency to rheumatic fever 91
- Fatigability in rheumatic fever 112
- Fatty heart 5

- Fatty infiltration (degeneration) of heart, 6
- Fetal myocarditis as cause of congenital heart disease, 18
- Fever therapy
 in bacterial endocarditis, 135
 in rheumatic heart disease, 78
- Fibrillation and flutter, auricular, caused by digitalis, 1139
- Fibrillation auricular, 10 69, 269, 613 780
- Fibrillation ventricular, 11, 658
- Fibrous of heart 6
- First heart sound, 509
- Fluoroscopy in congenital cardiac abnormalities, 35
- Flutter, auricular, 10 271 641, 775
- Flutter fibrillation, 776
- Food, relation to arteriosclerosis 1536
- Foramen ovale patent, 15, 27
- Formication in arteriosclerosis obliterans, 1702
- Form of electrocardiogram, 553
- Functional classification of patients with organic heart disease, 1018
- Functional disease of cardiovascular system, 9

G

- Gallop rhythm
 and the third heart sound, 526
 in chronic pulmonary heart disease 228
- Galvanometer, string, 604
- Gangrene
 in arteriosclerosis obliterans 1704
 in Raynaud's disease, 1736
- Gastrointestinal system in shock 1388
- Genitourinary system in shock, 1389
- Gigantism, 237
- Glomerulonephritis capillaries in 1562
- Glomerulonephritis chronic, 241
- Glomerulonephritis in bacterial endocarditis, 127
- Glucose intolerance as suggestive heart failure* 1087
- Glycosuria renal and hypotension 1531
- Gravim Steel murmur of pulmonic insufficiency 382
- Gummata of heart muscle 146

H

- Heart and deficiency diseases, 1272
- Heart and hypotension 1513 1515
- Heart and pericardium surgery of 1145

- Heartbeat disturbances of 718
 classification of disturbances of physiologic
 mechanisms of heartbeat 726
 clinical types and differentiation 728
 differential diagnosis 729
 effects of nervous control 725
 examination of pulse and heartbeat 720
 special anatomy and physiology of heart 720
- auricular fibrillation 780
 diagnosis 781
 etiology, 783
 pathogenesis 783
 pathology 783
 prognosis 784
 symptoms and complications 783
 treatment 786
- auricular flutter 775
- auriculoventricular rhythm 751
 diagnosis 756
 prognosis 756
 therapy 756
- disorders of impulse conduction 787
 heart block 787
 diagnosis 790
 etiology 789
 pathological physiology 790
 prognosis 791
 symptoms 790
 treatment 791
- Adams-Stokes disease 793
- alternation 798
- auriculoventricular block 788
- bundle branch block 799
- complete heart block, 792
- partial heart block 789
- sinoauricular heart block 788
- ectopic regular rhythms 753
- extrasystolic arrhythmia extrasystoles
 ectopic premature contractions or
 systoles intermittency of pulse 760
 diagnosis 762
 prognosis 763
 symptoms 762
 treatment 761
- heterogenic ectopic regular and irregular
 rhythms 757
- paroxysmal tachycardia 769
 diagnosis 767
 prognosis 771
 symptoms and complications 766
- Heartbeat disturbances of
 paroxysmal tachycardia (*continued*)
 treatment 773
- sinus arrhythmia 749
 diagnosis 752
 prognosis 753
 treatment 753
- sinus bradycardia 739
 diagnosis 748
 etiology 740
 prognosis 749
 treatment 749
- sinus tachycardia 731
 diagnosis 732
 prognosis 738
 temporary or transient sinus tachycardia 731
 treatment 738
- Heartbeat normal mechanism of and its
 disturbances 9
- Heart block 271 781
 acquired complete 22
 auriculoventricular 646
 congenital 21
 sinoauricular 653
- Heart chambers x ray visualization 711
- Heart compression of 1148
- Heart contusions of 1157
- Heart disease chronic total third degrees in
 treatment 1230
- Heart disease congenital 14
- Heart disease prevention and relief of as a
 public health problem 1023
 etiology 1023
 prevention 1023
 work and origin of American Heart Asso-
 ciation 1029
 activities of 1038
 aims 1046
 method of work 1041
- Heart failure congestive 296 112 1060
- Heart measurement by roentgenology 712
- Heart murmurs normal 481
- Heart muscle extract in arteriosclerosis
 obliterans 1718
- Heart pains 1509
- Heart penetrating wounds of 113
- Heart rate table for calculation of C12
- Heart sounds 507
 first heart sound 509
 splitting of first sound 515

- Heart sounds (*continued*)
 gallop rhythm and the third heart sound, 526
 clinical characteristics 533
 mechanism 533
 physiological third heart sound 536
 summation gallop rhythm, 530
 midsystolic click 524
 opening snap of mitral stenosis 541
 protodiastolic sound associated with calcification of pericardium, 538
 second heart sound, 522
 splitting of second sound 523
 semilunar opening click 541
 sounds associated with auricular contraction 547
 sounds in which air plays a part 541
 pericardial knock 545
 sounds due to mediastinal emphysema, 546
 splashing sound, 545
 water wheel murmur, 544
 systolic gallop rhythm 539
- Heart, special anatomy and physiology, 721
- Heat in treatment of arteriosclerosis obliterans 1717
- Height and surface area, effect on blood pressure 1336
- Hematogenic phlebophlebitis 1633
- Hematuria and rheumatic fever 117
- Hemopericardium 1164
- Hemoptysis in mitral stenosis 365
- Heparin
 in bacterial endocarditis, 135
 in shock, 1401
 in sudden arterial occlusion 1618
- Heredity and arteriosclerosis, 1559
- Herpes zoster capillaries in, 1363
- Histaminase
 in erythralgia 1614
 in hypertension 1462
- Histamine flare tests, 1708
- Histanoxia 1421
- Homatropine bromethylate (novatropine) in heart block 791
- Hookworm disease anemia associated with, 210
- "H substance" 1353
- Hydrotherapy, 1304
- Hypercalcemia electrocardiogram in, 679
- Hyperinsulinism 267d
- Hyperparathyroidism, 261
- Hyperpotassemia in shock, 1392
- Hypertension as cause of cardiac hypertrophy, 5
- Hypertension capillaries in, 1362
- Hypertension, electrocardiogram in 682
- Hypertension, essential, 213
- Hypertension in hypothyroidism, 263
- Hypertension, pulmonary 215
- Hypertension, roentgen appearance of heart 708
- Hypertensive arterial disease, 213, 1413
 cardiac symptoms, 1436
 consequences, 1431
 neurologic consequences 1438
 renal consequences, 1443
 renal concentration test 1414
 diagnosis, 1416
 disability, 1414
 etiology, 1422
 table of etiologic factors, 1421
 incidence, 1413
 mortality and causes of death 1414
 pathogenesis, 1427
 stages of hypertensive disease, 1432
 pathologic physiology, 1417
 control of arteriolar tone, 1420
 peripheral resistance, 1418
 results of arteriolar constriction, 1420
 pathology 1432
 prognosis 1448
 amyl nitrite test, 1450
 psychic factors, 1438, 1474
 emotional relations, 1489
 meaning of psychogenic, 1486
 methods of approach to problem 1474
 methods of study, 1475
 plan of therapeutic procedure 1493
 time element 1480
 diet 1485
 social climate and attitude, 1482
 symptoms, 1415
 treatment, 1455
 aid to tissue nutrition and respiration 1467
 therapy directed against etiology 1461
 diet, 1457
 fluid intake, 1458
 tobacco alcohol and coffee 1458

- Hypertensive arterial disease
 treatment (continued)
 therapy to reduce burden of injured structures 1459
 medicinal measures 1461
 physical measures 1465
 psychological measures 1460
 rest 1459
 surgical measures 1466
- Hypertensive heart disease physical therapy in 1317
- Hyperthyroidism electrocardiogram in 679
- Hyperthyroidism heart in 179
 auricular fibrillation 184
 description 180
 dilatation and hypertrophy 185
 effects of thyrotoxicosis 190
 treatment 191
- Hypertrophy of heart 6 529
- Hypertrophy of heart primary congenital 14 20
- Hypocalcemia electrocardiogram in 678
- Hypoglycemia as possible cause of hypotension 1552
- Hypoglycemia electrocardiogram in 678
- Hypoparathyroidism 260
- Hypophysis diseases of and the heart 277
- Hypoplasia of aorta 14 26
- Hypotension arterial 1498
- Hypotension capillaries in 1362
- Hypothyroidism as cause of cardiac dilatation and weakness 3
- Hypothyroidism (myxedema heart) 262
 clinical manifestations 263
 angina pectoris 265
 cardiac decompensation 264
 cardiac irregularities 265
 electrocardiogram in 679
 electrocardiographic changes 266
 enlargement of heart 265
 functional disturbances 265
 hypertension 265
 pathology 262
 treatment 266
- I
- Isoventricular rhythm 11 757
- Iliofemoral thrombophlebitis 1661
- Immune transfusions in bacterial endocarditis 135
- Inanition and the heart 1251
- Industry cardiacs in 1018
- Infarction following pulmonary embolism 218
- Infarction of heart 6
- Infarction of lateral wall of left ventricle 673
- Infections acute and hypotension 1527
- Infections electrocardiogram in 679
- Infections relation to arteriosclerosis 1556
- Infectious diseases thrombophlebitis as a complication 1655
- Inflammatory rheumatism a cause of heart disease 2
- Influenza and hypotension 1 27
- Influenza heart a monomer 2
- Injuries severe thrombophlebitis as a late complication 165
- Insect bites capillaries in 1363
- Inspection of precordium 472
- Inspiratory distention followed by expiratory diminution of the cardiac silhouette in chronic pulmonary heart disease 229
- Interauricular septum defects of 26
- Intermittency of pulse 760
- Intermittent pulse 475
- Intermittent venous hypertension in treatment of arteriosclerosis obliterans 1722
- Internal secretion glands of heart in 257
 pancreas 261
 diabetes 261
 hyperinsulinism 261
 parathyroids 259
 hyperparathyroidism 261
 hypoparathyroidism 260
 pituitary 257
 acromegaly and gigantism 257
 briophism 258
 insufficiency 257
 sex glands 266
 suprarenals 262
 Addison's disease 262
 benign chromaffin cell tumors 262
 cortical tumors and hyperplasia 262
 thymus 265
 status thymicolymphaticus 265
- Intertrabecular spaces 466
- Interventricular septum absence of 29
- Interventricular septum localized defect of 27
- Intoxications electrocardiogram in 679
- Intraventricular block 11 616
- Intraventricular block 11 561

- Intraventricular conduction defect complete 795
 Introduction to diseases of the cardiovascular system 1
 Inverted T waves 627
 Iodides
 in cardiovascular syphilis 172
 in hyperthyroidism, 193
 in temporal arteritis 1684
 Ipecac in paroxysmal tachycardia 774
 Irritability of heart, 4
 Lethal heart of soldiers 201
 Ischemic necrosis of heart 6

J

- Joints in rheumatic fever 102
 Junctional rhythm 754

K

- Karell diet
 in congestive heart failure 1095
 modification of, 1095
 Kidney consequences of arterial hypertension 1415
 Kidney lesions in bacterial endocarditis 127
 Kidneys cardiovascular system with relation to 254
 congestive heart failure 236
 essential hypertension, 215 1115
 etiology, 253
 pathogenesis 217
 prognosis 251
 treatment 251
 glomerulonephritis chronic 211
 nephritis acute 239
 Kissing lesions 126

L

- Late cyanosis 15
 Latent arteriosclerosis 215
 Leads in electrocardiography 60
 Left auricle double 23
 Left ventricular failure and paroxysmal cardiac dyspnea 1112
 left ventricular failure 1112
 paroxysmal cardiac dyspnea acute 1115
 attack 1115
 incidence 1111
 precipitating factors 1115
 prognosis 1116

Left ventricular failure (*continued*)
 therapy, 1117

- left ventricular failure in general 1117
 paroxysmal cardiac dyspnea 1117
 treatment between attacks 1121
 treatment of attack, 1118
 Left ventricular failure in coronary artery disease treatment, 494
 Leukocyte count in rheumatic fever 114
 Levocardiogram 579
 Lissak's disease anomalous development of capillary bed in cerebellar region in 1767
 Lipiodine in cardiovascular syphilis 172
 Liver pulse 354
 Local inflammatory thrombophlebitis 1655
 Low arterial pressure 1493
 clinical grouping of cases 1506
 definition 1199
 etiology 1501
 incidence 1501
 in disease 1506
 in health 1501
 Low arterial pressure from standpoint of human constitution 1511
 anatomical and pathanatomical panel 1511
 age, 1511
 body weight and build 1511
 cardiovascular system, 1513
 respiratory system 1515
 sex 1511
 immunological pathoimmunological panel 1527
 acute colds, 1527
 acute infectious diseases 1527
 chronic and focal infections 1529
 diabetes 1530
 influenza 1527
 pneumonia 1527
 syphilis 1529
 tuberculosis 1528
 tuberculosis 1529
 typhoid fever 1528
 Physiological and pathophysiological panel 1511
 blood
 anemia 1516
 pernicious anemia 1517
 blood sugar 1517
 chloride metabolism 1519

- Low arterial pressure
 from standpoint of human constitution
 physiological and pathophysiological
 panel (continued)
 climate 1526
 endocrines 1520
 heart 1515
 nervous system 1516
 occupation 1526
 oxygen and capillary circulation 1511
 posture 1521
 race 1520
 respiratory system 1514
 sleep 1524
 physiological considerations 1500
 adaptability of forces in circulation 1500
 energy index 1501
 present status 1498
 prognosis 1533
 symptoms 1507
 theories of causation of hypotension 1531
 glucose the fuel of life 1532
 treatment 1536
 general treatment 1537
- Lucic aortitis x ray diagnosis 701
- Lymphangitis 1620
- Lymphatism 267d
- Lymphedema of extremities 1616
 differential diagnosis 1623
 etiology 1616
 inflammatory lymphedema 1620
 general characteristics 1620
 primary lymphedema 1621
 secondary lymphedema 1621
 noninflammatory lymphedema 1617
 congenital lymphedema 1619
 primary lymphedema (lymphedema praecox) 1617
 secondary lymphedema 1619
 treatment
 medical treatment 1626
 treatment and prevention of inflammation 1627
 surgical treatment 1628
- M**
- Magnesium sulfate
 in paroxysmal auricular tachycardia 336
 in paroxysmal ventricular tachycardia 336
- Maladie de Roger 33
- Malignant hypertension 253 1448
- Maphursen (arsenoxide) in cardiovascular syphilis 169
- Massage in heart disease 1301
- Meals effect on blood pressure 1333
- Mechanical thrombophlebitis 1602
- Mechanotherapy in heart disease 1301
- Mecholyl iontophoresis in Raynaud's disease 1737
 technic 1738
- Mecholyl in paroxysmal auricular tachycardia 336
- Medial cystic necrosis 4
- Media of aorta syphilitic necrosis 140
- Mediastinal distortion in etiology of chronic pulmonary heart disease 220
- Mediastinal emphysema heart sounds due to 546
- Menstruation effect on blood pressure 1334
- Mental disease and acrocyanosis 1743
- Mercuripurin
 in chronic constrictive pericarditis 315
 in congestive heart failure 1088
 in edema 1815
- Mercurial diuretics and albuminuria 237
- Mercury in cardiovascular syphilis 168
- Metabolic products relation to arteriosclerosis 1536
- Midsystolic click 514
- Midsystolic short loud crepitating heart sound 546
- Milk leg 1661
- Minute volume output of heart effect of hydrotherapy on 1300
- Mitral pulse 780
- Mitral stenosis opening snap of 711
- Mitral valve disease 363
 mitral insufficiency 360
 mitral stenosis 367
 congenital 21
 with interauricular insufficiency 20
- Monckeberg arteriosclerosis 1703 1517
- Mönckeberg's sclerosis 1710
- Morbus caeruleus 11
- Morphine in paroxysmal tachycardia 771
- Mortality statistics of rheumatic fever 86
- Murmurs normal heart 481
- Myocardial disease 6
- Myocardial infarction anterior as cause of left axis deviation 621
- Myocardial infarction on electrocardiogram in 612

Myocardial injury from trauma 276
Myocardial necrosis caused by diphtheria 2
Myocardial syphilis 116
Myocarditis rheumatic 16 50
Myocarditis syphilitic 157
Myogenous dilatation of heart 331
Myomalacic pericarditis 292
Mixedema electrocardiogram in 679
Mixedema heart see Hypothyroidism 262
Myxematous heart physical therapy in 1517
Myxoma of auricle 4

N

Necrosis ischemic of heart 6
Necrosis medial cystic 4
Necrosis of myocardium caused by diphtheria 2
Necrotizing phlebitis 1662
Neocarphenamine
in bacterial endocarditis 135
in cardiovascular syphilis 169
Neocinchophen in rheumatic heart disease 73
Neoplasm of pericardium 7
Neoplasms of heart 1 6
Nephritic edema 1797
Nephritis acute 239
Nephritis acute electrocardiogram in 681
Nephritis chronic capillaries in 1562
Nephrotic edema 1797
Nervous system and hypotension 1516
Network of Chiari 22
Neurocirculatory asthenia 4 12 201
physical therapy in 1518
Neurologic consequences of arterial hypertension 1158
Neuromuscular system in shock 1559
Neuroses cardiac 5 196
clinical course and prognosis 203
diagnosis 203
etiology and pathogenesis 196
symptoms 200
association with organic heart disease 202
irritable heart of soldiers 201
pain 200
treatment 201
physical therapy 1518
Neurosis postphlebitic 1666
Neurovascular glomus tumors 1778

Nitroglycerin
in angina pectoris 415
in coronary insufficiency or the anginal syndrome 459
Nitroglycerol in hypertension 1462
Nodal rhythm 751
Nodal rhythm auriculoventricular 619
Node of His and Aschoff 723
Nodules subcutaneous in rheumatic fever 101
Normal electrocardiogram 555
Normal heart its output and circulatory rate 472
auscultation 478
normal murmurs 481
sounds 478
sternal crunch 480
systolic click 480
cardiac output 486
circulatory rate 487
inspection 472
palpation 471
percussion 476
pulse 474
rate 476
rhythm 475
tension 476
vessel wall 476
volume 475
x ray measurement of heart 483
Normal heart murmurs 191
Notching and slurring of Q R S complex 620
Notching of Q R S 391
Notching of T waves 625
Nourishment of heart by channels other than coronary arteries 463
artificial production of an accessory circulation of heart muscles 469
extracardiac anastomoses 463
nourishment by reversal of flow in cardiac veins 468
thoracic vessels 466
anatomic connections and physiology 466
embryology 466
Nourishment in congestive heart failure 108
Nutritional edema 1809

O

Obesity and heart disease 5
Obstetrics in the cardiac patient 201

- Occlusion of arteries sudden 1632
 Occupational therapy, 1314
 Occupation and hypotension 1526
 Operations on valves of heart 1182
 Oppression substernal as symptom of cardio
 vascular syphilis 147
 Orthodiagraphy 689
 Orthopnea in congestive heart failure 1063
 Orthostatic or postural hypotension 1522
 Oscillograph electrocardiograph 604
 Oscillographic readings to determine potency
 of major vessels and level of their
 occlusion 1703
 Ostium primum persistent 27
 Ouabain in congestive heart failure 1083
 Overstrain primary cardiac 281
 Oxygen
 in abnormal rhythm of hyperthyroidism
 192
 in acute pulmonary heart disease 221
 in chronic pulmonary heart disease 231
 in congestive heart failure 1056
 in coronary thrombosis 426

P

- Pacemaker 723
 Pacemaker wandering 9
 Pacemaking function disturbances of 10
 Pains cardiac 1509
 Palpation of precordium 174
 Pancreas diseases of and the heart 267c
 Pancreatic tissue extract in arteriosclerosis
 obliterans 1718
 Papaverine
 in acute pulmonary heart disease 221
 in sudden arterial occlusion 1648
 Paracentesis
 in chronic constrictive pericarditis 315
 in congestive heart failure 1100
 Paracentesis pericardial 305
 Parathyroids and the heart 239
 Paravertebral sympathetic block for relief of
 pain in angina pectoris 1183
 Paredrinol in prevention of syncope caused
 by administration of nitrite 1403
 Paroxysmal cardiac dyspnea 1112
 Paroxysmal dyspnea
 as symptom of cardiovascular syphilis 147
 in coronary artery disease treatment 401
 Paroxysmal dyspnea torsal thyroidectomy in
 1235
 Paroxysmal tachycardia 10 763
 diagnosis 737
 ventricular caused by digitalis 1140
 Partial heart block 789
 Passive congestion chronic in rheumatic
 heart disease 48
 Passive exercise in heart disease 1900
 Penetrating wounds of heart 1153
 Per Abrodil in use in angiocardiology 36
 Percussion of precordium 476
 Pericarditis nodosa 8 1568
 diagnosis 1574
 etiology 1568
 pathology 1568
 prognosis 1571
 symptoms 1571
 treatment 1575
 Pericardial adhesions x ray diagnosis 70c
 Pericardial defects 11 19
 Pericardial disease 7
 Pericardial effusion x ray diagnosis 70
 Pericardial knock 543
 Pericardial paracentesis 305
 Pericarditis
 acute pericarditis 288
 clinical problems peculiar to specific
 types of pericarditis 290
 differential diagnosis 300
 electrocardiogram 293 675
 etiology and classification 288
 pathologic anatomy 289
 pathologic histology 290
 myomatous pericarditis 291
 pyogenic pericarditis 291
 rheumatic pericarditis 290
 tuberculous pericarditis 291
 uremic pericarditis 291
 physical signs 293
 signs resulting from
 cardiac tamponade 297
 enlarged pericardial sac 291
 symptoms 292
 treatment 301
 Chronic constrictive pericarditis 303
 course and prognosis 311
 diagnosis 309
 differential diagnosis 313
 etiology and pathology 305
 treatment 315
 surgical treatment 316

- Pericarditis (*continued*)
 purulent pericarditis 1165
 rheumatic 48 51
 traumatic 275
- Pericardium and heart surgery of 1145
- Pericardium calcification of protodiastolic heart sound associated with 538
- Peripheral arterial atheroma and sclerosis as cause of vascular disease 4
- Peripheral arteries aneurysm of 1688
- Peripheral arteries disease of 8
- Pernicious anemia and hypotension 1516
- Pernicious anemia and the heart 1257
- Perpetual arrhythmia 780
- Perthes test 1781
- Petechial lesions as symptom of bacterial endocarditis 129
- Phasic arrhythmia 749
- Phlebosclerosis 1550
- Phlegmasia alba dolens 1664
- Phyllitis in congestive heart failure 1088
- Physical therapy in cardiovascular disease 1294
 etiology of cardiovascular disease and indications for physical therapy 1315
 cardiovascular syphilis 1316
 congenital cardiovascular defects 1315
 deficiency diseases 1317
 degenerative heart diseases 1317
 myxedematous heart 1317
 neurocirculatory asthenia and cardiac neuroses 1318
 pulmonary heart disease 1318
 rheumatic heart disease 1316
 thyrotoxic cardiovascular disease 1316
- exercise 1297
 Schott exercises 1299
- hydrotherapy 1304
 effects on
 blood pressure 1309
 minute volume output of heart 1309
 pulse 1308
 respiration 1310
 respiratory metabolism 1310
 skin capillaries 1309
 skin physiology 1311
 venous circulation 1309
 results of treatment 1312
 occupational therapy 1314
- Physical therapy in cardiovascular disease (*continued*)
 passive exercise 1300
 massage 1301
 mechanotherapy 1301
 rest 1297
 sources available for administration of physical therapy 1318
- Pick's disease 7 305
- Pituitary diseases of and the heart 257
 acromegaly and gigantism 257
 basophilism 258
 insufficiency 257
- Plateau pulse of aortic stenosis 377
- Pleximeter 176
- Plexor finger 476
- P.M.I. (point of maximum intensity) 475
- Pneumonia and hypotension 1527
- Pneumonia electrocardiogram in 681
- Pneumonitis in rheumatic fever 112
- Pneumonitis rheumatic in etiology of chronic pulmonary heart disease 225
- Pneumopericardium 7
- Poisons relation to arteriosclerosis 1556
- Polyarteritis nodosa 1568
- Polyarthritides as cause of heart disease 2
- Polycythemia capillaries in 1362
- Polycythemia in congenital cardiac abnormalities 30
- Port wine stain 1753
- Possible heart disease 6
- Postoperative thrombophlebitis 1654
- Postpartum thrombophlebitis 1654
- Postphlebotic neurosis 1666
- Posture and hypotension 1521
- Posture effect on blood pressure 1329
- Potential heart disease 6
- Precordial leads 630
 effects of digitalis on 1142
- Precordial pain in rheumatic fever 107
- Pregnancy
 care of heart disease in 502
 effect of pregnancy on normal heart 501
- Pregnancy congestive heart failure in 1101
- Pregnancy effect on blood pressure 1331
- Premature beats 10
- Premature contractions or systoles 700
- Preponderance 584
- Prerenal deviation of water 1809
- Pressure suction boot treatment of arterial sclerosis of iliacs 1719

- Presystolic gallop rhythm 527
 P R interval 562
 abnormalities of 615
 Protodiastolic gallop rhythm 529
 Protodiastolic heart sound associated with
 calcification of pericardium 538
 Protodiastolic pericardiac vibration 539
 Pseudo reduplication of second heart sound
 525
 Psychic factors in arterial hypertension 1138
 1474
 Psychic shock 1407
 Pulmonary and tricuspid stenosis congenital
 15
 Pulmonary arteriosclerosis in etiology of
 chronic pulmonary heart disease 22
 Pulmonary artery and branches disease of 8
 Pulmonary artery anomalies of 15
 Pulmonary artery dilatation of in hyper-
 trophy and dilatation of right ven-
 tricle 27
 Pulmonary artery x ray visualization 696
 Pulmonary atresia 28
 Pulmonary disease heart in 215
 acute pulmonary heart disease 215
 clinical features 217
 diagnosis 220
 etiology 215
 treatment 220
 chronic pulmonary heart disease 221
 clinical features 226
 diagnosis 230
 etiology 220
 bronchial asthma 224
 mediastinal distortion 225
 nontuberculous pulmonary fibrosis 223
 pneumoconiosis 223
 pulmonary arteriosclerosis 225
 pulmonary emphysema 222
 pulmonary tuberculosis 222
 rheumatic pneumonitis 225
 syphilis of pulmonary arteries 226
 incidence 221
 studies of circulatory function 230
 treatment 231
 Pulmonary embolism as cause of acute cor-
 pulmonale 216
 Pulmonary embolism electrocardiographic
 changes in 218
 Pulmonary embolism electrocardiography
 677
 Pulmonary heart disease 215
 physical therapy in 1318
 Pulmonary hypertension on 215
 as cause of right heart failure 3
 Pulmonary infarction roentgenologic
 evidence of 218
 Pulmonary valve bicuspid 24
 Pulmonary valvular disease 7 381
 pulmonic insufficiency 381
 pulmonic stenosis 382
 with closed ventricular septum 28
 Pulse 474 also see Heartbeat
 disturbances of 718
 Pulse deficit 784
 Pulse effect of hydrotherapy on 1308
 Pulse rate in rheumatic fever 109
 Pulsus alternans 658 798
 Pulsus irregularis perpetuus 780
 Pulsus paradoxus 298
 Purkinje fibers or arborizations 723
 Purulent pericarditis 1165
 P wave effects of digitalis on 1136
 P wave lowering fluttering or inversion of 9
 waves 615
 Pyogenic pericarditis 291 300
- ## Q
- Q R S and T waves abnormalities of in
 rheumatic carditis 61
 Q R S complexes abnormalities of 616
 Q R S deflections abnormally large or small
 591
 Q R S interval 563
 Q T interval 567 610
 abnormalities of 626
Quinidine in cardiac irregularities 1195
 accidents and sudden death 1224
 action of drug 1195
 contraindications 1197
 in auricular fibrillation 615 1206
 of hypertension 192
 in auricular flutter 615 1213
 in coronary
 occlusion 1219
 thrombosis 476 1220
 in licaions 1196
 in extrasystoles 1217

Quinidine in cardiac irregularities

(continued)

- in nodal tachycardia 1218
 - in paroxysmal
 - auricular tachycardia 326 1215
 - tachycardia 774
 - ventricular tachycardia 326 1218
 - in rheumatic heart disease 1209
 - in thyrotoxicosis 1210
 - in toxic goiter 1209
 - methods of administration 1201
 - reasons for failure 1222
 - temporary and enduring results 1206
 - auricular fibrillation 1206
 - auricular flutter 1213
 - extrasystoles 1217
 - nodal tachycardia 1218
 - paroxysmal auricular tachycardia 1215
 - ventricular tachycardia 1218
 - toxic symptoms 1222
 - types of arrhythmias 1193
- Quinine dihydrochloride in paroxysmal
auricular tachycardia 1216
- Q waves prominent 616

R

- Race and arteriosclerosis 1553
- Race and hypotension 1525
- Racket bursts of venous insufficiency of
saphenous system 1776
- Rash of rheumatic fever 105
- Raynaud's disease capillaries in 1362
- Raynaud's syndrome 1729
 - etiology 1731
 - arsenic 1735
 - cold 1731
 - disturbed calcium metabolism 1735
 - emotion 1732
 - occlusive arterial disease 1733
 - repeated vibration or percussion stimuli
1732
 - sex hormones 1735
 - pathology and pathologic physiology 1729
 - signs symptoms and course 1733
 - gangrene 1736
 - pre Raynaud's syndrome 1733
 - scleroderma (sclerodactylia acrosclerosis)
1735
 - trophic changes 1735

Raynaud's syndrome (continued)

treatment 1736

methohyl iontophoresis 1737

protection 1736

surgery, 1740

tobacco 1739

treatment of local conditions 1737

vasodilating drugs 1739

Recurrent idiopathic thrombophlebitis
(thrombophlebitis migrans), 1616

Reduplication of heart sounds 179

Reflex vasodilation tests 1706

Renal concentration test 1411

Renal consequences of arterial hypertension
1443

Renal decapsulation Ekebohm's for essential
hypertension 250

Renal glycosuria and hypotension 1531

Renal lesions in bacterial endocarditis 127

Respiration effect of hydr therapy on 1310

Respiration in shock 1590

Respiratory arrhythmia 749

Respiratory system and hypotension 1713

Rest in heart disease 1297

Resuscitation of heart from standstill and
from ventricular fibrillation 1181

Retinal pistol shot pulse in aortic insuffi-
ciency 376

Rhabdomyoma congenital 14 21

Rheumatic fever as cause of heart disease 2

Rheumatic fever electrocardiogram in 180

Rheumatic fever epidemiology of 61

bacteriology 87

epidemics 91

general prevalence 81

predisposing causes 83

age 83

anthropological type 91

familial prevalence 91

geographical and climatologic 89

racial susceptibility 91

social and living conditions 90

Rheumatic fever evaluation of active infec-
tion 94

clinical evidence of active disease 101

abdominal pain 112

chorea 107

congestive failure 115

epistaxis 109

erythemas 107

Rheumatic fever

clinical evidence of active disease (*continued*)

- exercise tolerance 112
- fever 101
- joints 102
- pneumonitis 112
- precordial pain, 107
- pulse rate 109
- subcutaneous nodules 101
- weight 110

laboratory evidence 111

- blood changes 111
- electrocardiographic changes 116
- urinary changes 117

subclinical recurrences 118

Rheumatic heart disease 42

course of disease 53

- acute fulminating type 53
- chronic active type 55
- persistently inactive type 58
- recurring form 57

diagnosis 64

differential diagnosis 65

electrocardiographic findings 59

- active carditis 59
- inactive rheumatic heart disease 63

etiology 46

incidence 44

prognosis 66

- immediate attack 66
- ultimate outcome 67
 - age at onset 68
 - auricular fibrillation 69
 - recurrent activity 71
 - severity of attack 69
 - sex 68
 - type of manifestation 68

structural changes 46

- chronic passive congestion 48
- endocarditis and valvulitis 47
- myocarditis 46
- pericarditis 48

subdivisions

- active rheumatic heart disease (carditis) 43
- inactive rheumatic heart disease 43

symptomatology 49

- active rheumatic heart disease (carditis) 49
 - signs and symptoms 52
- inactive rheumatic heart disease 49
- myocarditis 50

Rheumatic heart disease

symptomatology (*continued*)

- pericarditis 51
- physical signs 53
- valvulitis 50

treatment 71

- climatotherapy 76
- eradication of focal infection 77
- fever therapy 78
 - of carditis 71
 - of pericarditis 71
 - of subacute and chronic carditis 74
 - of convalescence 76
 - of inactive rheumatic heart disease 78
- physical therapy 1316
- prevention 78
- serums and vaccines 77

Rheumatic infection of heart or blood vessels 1

Rheumatic pericarditis 290 299

Rheumatic pneumonitis in etiology of chronic pulmonary heart disease 221

Rhythm abnormalities of in rheumatic carditis 61

Rhythm disorders of "r"

Rhythm of heart normal and changes of vagosympathetic origin 9

Rhythms ectopic regular 753

Rickets as cause of cardiac pathology 5

Right heart failure causes 5

Roentgenkymography 710

Roentgenology of heart and great vessels 688

anatomical considerations 690

individual chambers and vessels 691

position of patient 690

relations of esophagus trachea and bronchi to heart and great vessels 693

calcifications 693

cardiac configuration 710

congenital heart defects 706

coronary disease and sequelae 708

extrinsic causes of cardiac enlargement 708

measurements 712

aorta 711

heart 712

pericardial diseases, 705

special x ray methods 710

roentgenkymography 710

visualization of heart chambers and thoracic blood vessels 711

x ray methods 688

R T deviation in anteromycocardial infarction 663

Rumpel Leede test, 1360

Rupture of heart 7

Rupture of vessels 8

S

Salicylates in rheumatic heart disease 73

Salt and water deficiency and the heart 12, 6

Saltyrgan

in chronic constrictive pericarditis 31

in congestive heart failure 1098

in coronary artery disease 403

in edema 1815

Sanders oscillating bed in treatment of arteriosclerosis obliterans 1721

Scarlet fever electrocardiogram in 691

Schilling count in rheumatic fever 116

Schott exercises 1299

Scleroderma (sclerodactylia acrosclerosis) in Raynaud's disease 1735

Sclerosis Monckebergs 1710

Sclerosis of valves 7

Sclerosis vascular 8

Scotch douche 1303

Scurvy and the heart 1291

Second heart sound 322

Sedimentation rate in rheumatic fever 115

Semilunar cusps anomalies of 11, 23

Semilunar opening click 313

Senility and cardiac changes 5

Septa anomalous 14

Septal defects 7

localized 26

Septum primum deflection to the left 23

Serums in treatment of rheumatic heart disease 77

Sex and low arterial pressure 1511

Sex effect on blood pressure 1315

Sex glands diseases of and the heart 267c

Shock 1381

capillaries in 1361

chemistry 1391

clinical picture 1391

definition 1382

etiology 1395

hypotension in 1516

pathology 1396

Shock (*continued*)

physiology 1387

cardiovascular 1397

gastrointestinal 1398

genitourinary 1399

neuromuscular 1399

respiration 1390

prognosis 1397

treatment 1398

Simmonds disease 257

Sinoauricular bradycardia 9

Sinoauricular heart block 635, 788

Sinoauricular node 722

Sinoauricular standstill 9

Sinoauricular tachycardia 9

Sinus arrhythmia 9, 633, 719

diagnosis 732

prognosis 753

treatment 753

Sinus bradycardia 635, 759

diagnosis 718

etiology 740

prognosis 749

treatment 719

Sinusoidal spikes 466

Sinus pauses prolonged (*canine standstill*), 635

Sinus tachycardia 731

diagnosis 732

prognosis 738

temporary or transient sinus tachycardia 731

treatment 738

Siomine in cardiovascular syphilis 172

Sitz bath in treatment of arteriosclerosis obliterans 1716

Skin capillaries effect of hydrotherapy on 1309

Skin physiology effect of hydrotherapy on 1311

Sleep and hypertension 1521

Sleep effect on blood pressure 1330

Slurring and notching of Q R S and T waves 620

Slurring of Q R S 591

Soaks in treatment of arteriosclerosis obliterans 1717

Sodium nitrite in hypertension 1462

Sodium salicylate in essential hypertension 251

- Soldier's heart 4 12 201
 Sounds heart 507
 Southey's tubes in treatment of edema 1818
 Spider bursts of venous insufficiency of
 saphenous system 1776
 Splashing sound 545
 Stab wounds of heart 1153
 Standstill sinoauricular 9
 Status thymicolymphaticus 267d
 Steering wheel injury to heart 4
 Sternal crunch 480
 Stokes Adams seizures electrocardiogram in
 684
 Stokes Adams syndrome 21
 Strawberry marks 1752
 Strax and DeGraff method of determining
 capillary pressure 1358
Streptococcus hemolyticus in etiology of
 rheumatic fever 87
 String galvanometer 601
 Strophanthus in congestive heart failure 1083
 Structural lesions of heart 6
 S T segment and T wave effects of digitalis
 on 1130
 S T segment deviation of 628
 S T segments and T waves abnormalities
 of 12
 Sturge Weber disease 1766
 St Vitus dance as cause of heart disease 2
 Substernal oppression as symptom of cardiac
 vascular syphilis 147
 Sudden embolism and thrombosis of arteries
 of extremities 1632
 Sulfanilamide
 in bacterial endocarditis 133
 in rheumatic heart disease 74
 Sulfo cyanide in hypertension 146^a
 Summation gallop rhythm 530
 Suppurative thrombophlebitis 1633
 Suprarenals and the heart 26^a
 Surface temperature studies 1706
 Surgery in the cardiac patient 492
 Surgery of heart and pericardium 1113
 cardiac compression due to scars 1169
 diagnosis 1170
 etiology 1169
 operation for removal 1171
 postoperative care 1172
 results obtained after resection 1173
 Surgery of heart and pericardium (*continued*)
 classification of heart disease 1147
 collateral blood supply to heart produc-
 tion of 1178
 Beck operation results of 1180
 ligation of coronary veins for coronary
 sclerosis, 1180
 vascular anastomoses produced by chem-
 ical agents 1180
 vascularized grafts for coronary artery
 sclerosis 1179
 compression of heart 1148
 acute compression triad 1150
 chronic compression triad 1152
 physiology 1148
 hemopericardium 1164
 ligation of patent ductus arteriosus 1174
 operative procedure 1176
 results after ligation 1177
 selection of patients 1175
 operations on cardiac valves 1182
 purulent pericarditis 1163
 resuscitation of heart from standstill and
 from ventricular fibrillation 1181
 trauma 1153
 nonpenetrating wounds or contusion of
 heart 1157
 incidence of cardiac contusions 1161
 symptoms and diagnosis 1161
 treatment 1164
 penetrating wounds of heart 1153
 diagnosis 1154
 treatment 1154
 S waves deep in Lead II with left axis
 deviation significance of 625
 Sydenham's chorea and rheumatic fever 107
 Sydenham's chorea as cause of heart disease
 2
 Syncope cardiac electrocardiogram in 681
 Syncope in congenital cardiac abnormalities
 30
 Syphilis and hypotension 1529
 Syphilis as cause of cardiovascular disease 3
 Syphilis cardiovascular 133
 age and race 143
 complications 149
 aneurysm 151
 of aortic arch 154

- Syphilis cardiovascular
 complications (*continued*)
 aortic insufficiency 150
 occlusion of coronary artery 159
 syphilitic myocarditis 157
 diagnosis 159
 aneurysm 162
 aortic insufficiency 161
 etiology 138
 pathology 143
 physical signs 148
 prevalence and distribution 140
 symptoms 146
 treatment 161
 appraisal 166
 available drugs and therapeutic agents 163
 effects of treatment 176
 fundamental principles 163
 general treatment measures 172
 preventive aspects 177
 special considerations 174
 aortitis and aneurysm 174
 coronary sclerosis and myocarditis 175
 peripheral vascular disease 176
 Syphilis of myocardium 146
 Syphilis of pulmonary arteries in etiology of chronic pulmonary heart disease 226
 Syphilitic aortitis x ray diagnosis 701
 Syphilitic myocarditis 157
 Systolic click 480

T

- Tachycardia auricular paroxysmal 638
 Tachycardia nodal paroxysmal 612
 Tachycardia paroxysmal 10 763
 diagnosis 737 767
 prognosis 771
 symptoms and complications 766
 treatment 713
 Tachycardia sinoauricular 9
 Tachycardia sinus (simple) 731
 Tachycardia ventricular diagnosis 738
 Tachycardia ventricular paroxysmal 636
 caused by digitalis 1140
 Tamponade cardiac 305
 T and Q R S waves abnormalities of in rheumatic carditis 61
 T deflection 592
 Teleoroentgenography 689

- Telesystolic extracardiac sound 323
 Temperature effect on blood pressure 1336
 Temporal arteritis 1681
 diagnosis and prognosis 1682
 differential diagnosis 1681
 etiology 1681
 pathology, 1682
 treatment 1684
 Tetralogy of Fallot 15 21 23
 x ray diagnosis 707
 Theobromine
 in angina pectoris 414
 in congestive heart failure 1088
 in coronary artery disease 399
 in edema 1814
 in essential hypertension 234
 Theocain in congestive heart failure 1088
 Theophylline (theocin)
 in angina pectoris 414
 in congestive heart failure 1088
 in coronary artery disease 399
 in coronary thrombosis 426
 in edema 1814
 in essential hypertension 234
 Theophylline ethylenediamine in paroxysmal cardiac dyspnea 1119
 Thesbian vessels 466
 Thevenin in congestive heart failure 1081
 Thiocyanate in hypertension 3 8
 Thoracic aneurysm 1687
 Thoracic blood vessels x ray visualization 711
 Thoracotomy in congestive heart failure, 1101
 Thromboangiitis obliterans 1579
 capillaries in 1563
 classificatory objectives 1602
 distinguishing typifying peculiarities 1603
 clinical amplification 1591
 universality of lesions 1593
 clinical concept 1579
 clinicopathological acceptance 1580
 enigma of vascular disease 1583
 equivocalness of observational information 1601
 pathological concept 1582
 Thrombophlebitis 1611
 clinical symptoms and signs 1661
 complications and sequelae 1663
 diagnosis 1666

- Thrombophlebitis (*continued*)
 etiology, 1651
 chemical thrombophlebitis 1652
 hematogenic thrombophlebitis 1653
 local inflammatory thrombophlebitis 1653
 mechanical thrombophlebitis 1652
 primary thrombophlebitis 1656
 idiopathic thrombophlebitis of nonre-
 curring type 1657
 recurrent idiopathic thrombophlebitis
 (thrombophlebitis migrans) 1656
 thromboangitis obliterans 1656
 secondary (complicating) thrombophle-
 bitis 1651
 postoperative thrombophlebitis 1651
 postpartum thrombophlebitis 1655
 thrombophlebitis as a late complica-
 tion of severe injuries 1655
 thrombophlebitis complicating infec-
 tious disease 1655
 thrombophlebitis complicating nonin-
 fectious systemic diseases 1656
 suppurative thrombophlebitis 1653
 varicose thrombophlebitis 1653
 pathologic physiology 1639
 pathology 1657
 treatment 1667
 chronic venous insufficiency 1673
 hematogenic thrombophlebitis 1669
 local thrombophlebitis 1667
 postphlebitic neurosis 1673
 primary thrombophlebitis 1673
 secondary thrombophlebitis 1668
 Thrombophlebitis migrans, 1656
 Thrombosis 8
 Thrombosis and embolism of arteries of ex-
 tremities sudden 1632
 Thymus diseases of and the heart 267d
 Thyroid disease as cause of cardiovascular
 diseases 3
 Thyroidectomy in coronary artery disease 403
 Thyroidectomy total in congestive heart
 failure 1101
 Thyroidectomy total in treatment of chronic
 heart disease 1230
 physiology 1230
 results 1232
 comparison of results in congestive fail-
 ure and angina pectoris 1234
 Thyroidectomy total
 results (*continued*)
 comparison of results obtained by other
 methods of treatment 1235
 technique 1238
 operative technique 1240
 postoperative management and super-
 vision 1242
 preoperative preparation 1240
 selection of cases 1239
 Thyroid extract
 in hypothyroidism 266
 in secondary thrombophlebitis 1668
 Thyroid operations anesthesia for 193
 Thyrotoxic cardiovascular disease physical
 therapy in 1916
 Thyrotoxic heart 180
 Thyrotoxicosis 179
 as cause of cardiovascular disease 3
 effects of 190
 Thyroxin in nephrotic edema 1816
 Tigering 5
 Time relations of electrocardiogram compari-
 son of with certain mechanical
 events 611
 Tissue extract No. 568 (depropriner) 1718
 Tobacco effect on blood pressure 1335
 Tonogenous dilatation of heart 330
 Toxemias of pregnancy capillaries in 1362
 Transposition of great arteries 7
 Trauma of heart 4 268 1159
 compensation and trauma of heart 289
 contusion of heart 275
 angina pectoris 275
 myocardial injury 276
 pericarditis 275
 sudden death 276
 disorders of rhythm 269
 auricular fibrillation 269
 auricular flutter, 271
 extrasystolic arrhythmia 271
 heart block 271
 Primary cardiac overstrain 281
 management and treatment 285
 valvular disease 272
 from direct violence 273
 from strain 272
 wounds of heart 281
 Trendelenburg test 1779

- Trepopnea, 1116
 Trichinosis and hypotension, 1523
 Tricuspid and pulmonary stenosis congenital 15
 Tricuspid atresia, 29
 Tricuspid disease, 7 380
 Triloculate heart, 7
 Triple extrapolation method of measuring cardiac output, 486
 Truncus arteriosus, persistent, 15 29
 Tuberculosis and hypotension 1529
 Tuberculous pericarditis 291, 299
 T wave and S T segment effects of digitalis on, 1150
 T waves, abnormalities of 12 626
 Typhoid fever and hypotension 1528
 Typhoid heart a misnomer 2

U

- Undernutrition and the heart 1254
 Urea in edema, 1814
 Uremia electrocardiogram in 682
 Uremic pericarditis 291 300
 Uroguin 1011
 in congestive heart failure 1083
 Urinary changes in rheumatic fever 117
 Uroelectan B use in angiocardiology, 36
 Urticaria capillaries in, 1363
 U waves 629

V

- Vaccines in rheumatic heart disease 77
 Vagus arrhythmia 740
 Valve rupture 4
 Valves of heart operations on 1182
 Valvular deformity, 7
 Valvular disease
 from direct violence, 273
 from strain 272
 Valvular heart disease chronic 362
 aortic valve disease, 7, 373
 aortic insufficiency 161, 374
 in cardiovascular syphilis 150
 aortic stenosis, 21 377
 mitral valve disease 7 363
 mitral insufficiency 365
 mitral stenosis, 367
 congenital, 24
 with interauricular insufficiency, 25
 prognosis of chronic valvular disease, 393

- Valvular heart disease chronic (*continued*)
 pulmonary valvular disease, 7, 381
 pulmonic insufficiency, 381
 pulmonic stenosis, 382
 with closed ventricular septum 23
 tricuspid valve disease, 7, 380
 Valvular incompetency, 12
 Valvular lesions, relative frequency in rheumatism, 47
 Valvular sclerosis, 4
 Valvulitis, rheumatic, 47, 50
 Varicose thrombophlebitis 1633
 Varicose veins, 1770
 complications, 1782
 etiology, 1770
 symptoms and diagnosis, 1777
 test of venous circulation in varicose extremity, 1778
 Petthet test, 1781
 Trendelenburg test 1779
 treatment, 1786
 injection treatment, 1791
 type and amount of solutions used 1793
 Vascular anastomoses between heart and parietal pericardium produced by chemical agents, 1180
 Vascular anomalies, 1748
 cavernous aneurysm 1753
 cirsoid aneurysm, 1755
 congenital arteriovenous aneurysm, 1751
 port wine stain 1753
 simple angioma 1750
 treatment 1756
 Vascular disease, 7
 theories of etiology, 1585
 Vascular efficiency, faulty, 12
 Vascular system and hypotension, 1514
 Vasodilation tests reflex 1706
 Vena cava, superior x ray visualization 695
 Venesection
 in congestive heart failure, 1099
 in paroxysmal cardiac dyspnea, 1119
 Venous circulation effect of hydrotherapy on, 1309
 Venous engorgement in right-sided cardiac failure, 353
 Venous filling time, determination, 1701
 Venous insufficiency, chronic, treatment, 1673

- Venous pressure, 1367
 cardiac insufficiency, 1376
 direct method, 1369
 indirect method 1368
 relation between
 venous and arterial pressure, 1373
 venous pressure and cerebrospinal fluid pressure, 1372
 venesection, 1377
 venous pressure under normal conditions, 1371
- Ventricle, left x ray visualization, 697
- Ventricle, right, x ray visualization, 695
- Ventricular complex, 556
- Ventricular complexes relation of, in the three indirect leads, 610
- Ventricular escape, 9 652
- Ventricular extrasystoles 653
- Ventricular failure, left, 1112
- Ventricular fibrillation, 11, 658
- Ventricular gradient, 574
- Ventricular hypertrophy
 left as cause of left axis deviation, 621
 right, as cause of right axis deviation 625
- Ventricular ischemia, 12
- Ventricular paroxysmal tachycardia, 656
 caused by digitalis 1140
- Ventricular premature beats left, as cause of right axis deviation, 625
- Ventricular premature contractions right as cause of left axis deviation 625
- Ventricular, septal defect, 7
- Ventricular tachycardia diagnosis, 738
- Ventricular weakness, 12
- Verodigen, 1009
- Vichy douche, 1301
- Vocational possibilities for heart patients 1051
- ## W
- Wandering pacemaker, §
- Water and salt deficiency and the heart 1256
- Waterhammer (Corrigan) pulse in aortic insufficiency, 375
- Water wheel murmur, 511
- Weight change in rheumatic fever 310
- Weight, effect on blood pressure 1335
- Whirlpool baths in treatment of arteriosclerosis obliterans, 1717
- Widening of Q R S complexes 620
- Work tests, measured 1709
- Wounds of heart, 281
 penetrating wounds, 1153
- ## X
- X ray measurement of heart 185
- X ray methods 688